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**Factors influencing cold ischaemia time in deceased donor  
kidney transplants**

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## **Declaration**

I declare that the work presented in this thesis is my own and that it has not been submitted for any other degree or professional qualification except where stated otherwise by reference or acknowledgement. Part of the thesis has been published in the journal, Transplantation.

The author was a member of a research group led by her supervisor Professor Lorna Marson. I played a major role in collaborating with kidney transplant centres and histocompatibility and immunogenetics laboratories across the country to collect data. Data collection, input, univariate analysis and interpretation were entirely my own work with the exception of analysis of transport data that was carried out by Mr James Blackmur. Multivariate modelling and analyses were carried out by the statisticians at NHS Blood and Transplant.

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**Sussie Shrestha**

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**Dated**

## **Abstract**

Kidney transplant remains the optimal treatment for majority of patients with end stage renal failure. The major challenge facing the transplant community is the shortage of organs for donation as demand outstrips supply. This has led to a significant change in practice over the last decade with an increasing use of kidneys from deceased donors following circulatory death (DCD) and extended criteria donors (ECD) that are more susceptible to ischaemic injury.

A period of cold ischemia time (CIT) is an inevitable consequence of organ retrieval and transplantation in the process of deceased organ donation. It is well established that longer CIT is associated with poorer outcomes following kidney transplantation. It is also one of the few potentially modifiable risk factors. It is, therefore, crucial to identify and address the factors that adversely affect CIT to enable optimal utilisation of available kidneys.

The study investigated multiple factors affecting CIT, involving all aspects of kidney journey from retrieval to transplantation to identify areas for improvement.

The aims of the study are:

- To undertake comprehensive review of logistical factors in transplant centres in the United Kingdom (UK) and, their impact on CIT in deceased donor kidney transplants
- To determine whether there are specific areas to focus efforts on to reduce CIT
- To put forward proposals about how to reduce CIT across the UK

This is a prospective, longitudinal study over 14 months examining logistical pathway of deceased donor kidney transplants in the UK that includes kidney allocation, retrieval, transport, histocompatibility testing and preparation of recipients for transplantation.

Four sets of questionnaires were developed and utilised to encapsulate critical events along the kidney timeline with additional data input from the National Health Service Blood and Transplant (NHSBT).

Results identified a number of factors that affected CIT, the most important of which was adoption of a virtual crossmatch (vXM) policy where appropriate. CIT was also reduced significantly if pre-transplant crossmatch (pXM) was performed with donor pre-retrieval peripheral blood rather than donor tissues. Significant reduction also resulted from use of stored recipient blood for pXM rather than a current sample. Other factors that led to increase in CIT in the vXM group were travel times, recipients requiring haemodialysis immediately before transplantation and kidney re-allocation.

This study identifies specific factors that can be addressed to potentially minimise CIT and improve outcomes in deceased donor kidney transplants in the UK.

## **Lay summary**

The optimal treatment for majority of patients with end stage kidney failure is kidney transplantation. The ever-increasing demand for kidneys for transplantation has led to a significant change in practice with increasing use of kidneys that would previously have been deemed unsuitable for transplantation, such as kidneys from older donors (>60 years), donors with medical conditions such as heart disease and, donation after cessation of heartbeat as compared to those from beating-heart but brain-dead donors. These kidneys are more susceptible to injury from a period of cold storage known as cold ischaemia time (CIT) that which is inevitable in the process of transplantation from deceased donors. Longer CIT is associated with poorer outcomes following transplantation, such as delay in functioning and failure of transplanted kidney. It is, therefore, essential to keep CIT as short as possible to enable optimal utilisation of available kidneys.

The study examined multiple logistical factors affecting CIT, such as events at the donor hospital, the transport of kidneys to recipient hospital, work carried out in the laboratory to establish compatibility of the donor with the recipient, preparation of the recipients and availability of operating theatres and relevant staff.

The aims of the study are:

- To undertake comprehensive review of logistical factors associated with kidney transplants from deceased donors in the United Kingdom (UK) and their impact on CIT
- To determine whether there are specific areas to focus on to reduce CIT
- To put forward proposals about how to reduce CIT across the UK

This study involved prospective collection of data over 14 months, utilising four sets of questionnaires that were developed to encapsulate the critical events in the kidney timeline. Results identified a number of factors that affected CIT, most important of which was relating to transplants in whom compatibility testing between donor and recipient in the laboratory was omitted and was deemed safe to proceed without waiting for the test to be performed, known as virtual crossmatch (vXM). When the

test was performed before transplant, known as pre transplant crossmatch (pXM), the use of donor blood that was obtained prior to retrieval surgery and, the use of stored recipient blood rather than a current sample also reduced CIT significantly. In the vXM group, travel times, recipients requiring dialysis immediately before transplant and repeat allocation of kidneys to a different recipient were significant.

This study identifies important factors that impact on CIT that can be addressed to potentially minimise it and improve outcomes following kidney transplants from deceased donors in the UK.



## **Presentations and publication**

### **Presentations**

#### **Oral presentations:**

1. Medawar medal session, British Transplantation Society annual congress, Glasgow, 27 February 2014
2. School of surgery day, Royal College of Surgeons of Edinburgh, Edinburgh, 29 November 2013
3. NHS Blood and Transplant research and development annual conference, Oxford, 17-18 September 2012
4. Congress of the European Society of Organ Transplantation, Glasgow, 5 September 2011
5. British Transplantation Society annual congress, Glasgow, 22-24 February 2012
6. British Transplantation Society annual congress, Bournemouth, 9-11 March 2011

#### **Poster presentations:**

1. NHS Blood and Transplant research and development annual conference, Oxford, 16-17 September 2013

### **Publications arising directly from the work**

1. **Shrestha** S, Bradbury L, Boal M, Blackmur J, Watson C, Taylor C, Forsythe J, Johnson R, Marson L. Logistical factors influencing cold ischaemia times in deceased donor kidney transplants. Transplantation. 2016 Feb; 100(2): 422-8.

## Contents

<b>1</b>	<b>Introduction .....</b>	<b>1</b>
1.1	History of renal transplantation .....	1
1.2	Renal transplant versus dialysis .....	3
1.3	Deceased organ donation .....	4
1.4	Deceased donor kidney allocation policy .....	11
1.5	Principles of deceased donor kidney allocation scheme .....	13
1.6	Reallocation of kidneys .....	14
1.7	Logistics of kidney donation and transplantation in the United Kingdom 15	
1.7.1	National Health Service Blood and Transplant (NHSBT) and Organ Donation and Transplantation (ODT) .....	15
1.7.2	Specialist nurses for organ donation (SN-OD) .....	15
1.7.3	Kidney transplant centres .....	17
1.7.4	Histocompatibility and Immunogenetics laboratories .....	20
1.7.5	Transplant centre teams .....	23
1.8	Potential donors .....	23
1.9	Establishing donor and recipient compatibility .....	23
1.9.1	Determining donor and potential recipient HLA type .....	24
1.9.2	Potential recipient HLA antibody screening .....	24
1.10	Immediate pre-transplant donor- recipient compatibility assessment	25
1.10.1	Pre-transplant laboratory crossmatch test .....	26
1.10.2	Virtual crossmatch .....	26
1.11	Ischaemia-reperfusion injury .....	28
1.12	Delayed graft function .....	29
1.13	Kidney preservation (Machine perfusion versus cold storage) .....	31
1.14	Cold ischaemia time .....	33
1.14.1	Why is Cold Ischaemia Time important? .....	33
1.14.2	Implications of prolonged Cold Ischaemia Time on kidney transplant outcomes .....	35
1.14.3	What are the factors that affect Cold Ischaemia Time? .....	40
1.15	Summary .....	43
<b>2</b>	<b>Methodology .....</b>	<b>44</b>
2.1	Study design .....	44
2.2	Project collaboration .....	45
2.3	Measurements .....	45
2.4	Kidney timeline .....	46
2.5	Involvement of Organ Donation and Transplantation (ODT), NHS Blood and Transplant (NHSBT) and the Duty Office (DO) services .....	48
2.6	Data protection .....	49
2.7	Ethical approval .....	49
2.8	Pilot study .....	50
2.8.1	Participating centres in the pilot study .....	51
2.8.2	Findings of the pilot study and subsequent amendments .....	52
2.9	Questionnaires .....	52
2.10	Dissemination of study information .....	54
2.11	Multicentre engagement .....	54
2.11.1	Centre visits .....	54
2.11.2	Kidney transplant centres .....	55

2.11.3	Histocompatibility and Immunogenetics units.....	56
2.11.4	Regional donor transplant coordinator teams.....	57
<b>2.12</b>	<b>Deceased donor kidney transplant logistics .....</b>	<b>58</b>
2.12.1	Transplant centres .....	58
2.12.2	Histocompatibility and Immunogenetics units and virtual crossmatch policy .....	59
2.12.3	Transport.....	60
<b>2.13</b>	<b>Variation in local transplant centre practices .....</b>	<b>60</b>
<b>2.14</b>	<b>Crossmatching Description .....</b>	<b>63</b>
<b>2.15</b>	<b>Data Collection.....</b>	<b>64</b>
<b>2.16</b>	<b>Data Input.....</b>	<b>65</b>
<b>2.17</b>	<b>Data Cleansing and Quality Assurance .....</b>	<b>66</b>
<b>2.18</b>	<b>Statistical Analysis.....</b>	<b>66</b>
<b>2.19</b>	<b>Intercept Description .....</b>	<b>67</b>
<b>3</b>	<b>Results.....</b>	<b>68</b>
<b>3.1</b>	<b>Introduction.....</b>	<b>68</b>
<b>3.2</b>	<b>Review of current practices in UK transplant centres.....</b>	<b>70</b>
<b>3.3</b>	<b>Cold ischaemia time .....</b>	<b>72</b>
3.3.1	Cold ischaemic time by transplant centre.....	73
3.3.2	Cold ischaemic time in kidney-only and multi-organ transplant centres.....	75
3.3.3	Cold ischaemic time in relation to kidney allocation (Local/Import) .....	77
3.3.4	Cold ischaemic time in relation to reallocation of kidneys.....	79
<b>3.4</b>	<b>Donor factors and impact on cold ischaemia time.....</b>	<b>83</b>
3.4.1	Type of donor .....	83
3.4.2	Centre variation in cold ischaemia time .....	85
3.4.3	Timing of dispatch of donor blood for tissue typing in relation to duty office notification of potential donor.....	89
3.4.4	Donor HLA typing time .....	89
3.4.5	Timing of retrieval surgery .....	89
3.4.6	Timing of start of retrieval surgery (knife to skin) and kidney in ice box..	90
3.4.7	Timing of kidney offer in relation to retrieval surgery .....	90
3.4.8	Timing of kidney in ice box in relation to in situ cold perfusion at retrieval surgery.....	96
3.4.9	Timing of kidney collection in relation to kidney put in ice box.....	97
<b>3.5</b>	<b>Transport Factors and impact on cold ischaemia time .....</b>	<b>98</b>
3.5.1	Kidney travel distance .....	98
3.5.2	Variation in travel time and distance for DBD and DCD kidneys.....	101
3.5.3	Mode of transport of kidneys .....	104
<b>3.6</b>	<b>H&amp;I factors and impact on cold ischaemia time .....</b>	<b>109</b>
3.6.1	Crossmatching.....	109
3.6.2	Type of crossmatching for DBD and DCD kidney transplants.....	112
3.6.3	H&I laboratory variation in type of crossmatching .....	115
<b>3.7</b>	<b>Virtual crossmatch.....</b>	<b>119</b>
3.7.1	Timing of decision to proceed to transplant with a vXM in relation to in situ cold perfusion .....	121
<b>3.8</b>	<b>Pre-transplant crossmatch .....</b>	<b>122</b>
3.8.1	Donor tissue used for pre-transplant crossmatching .....	122
3.8.2	Recipient serum sample used for prospective crossmatching .....	129
3.8.3	Timing of reporting of pre-transplant crossmatch result in relation to latest of H&I staff arrival, donor sample arrival and recipient sample collected.	134

3.8.4	Timing of reporting of pre-transplant cross match result in relation to in situ cold perfusion .....	135
<b>3.9</b>	<b>Recipient preparation and impact on cold ischaemia time .....</b>	<b>136</b>
3.9.1	Recipient mode of travel to hospital for transplant.....	136
3.9.2	Requirement for haemodialysis immediately pre-transplant.....	138
3.9.3	Timing of contact of recipient for kidney transplantation after kidney offer accepted .....	142
3.9.4	Timing of arrival of recipient in hospital for transplantation after recipient contacted.....	143
3.9.5	Timing of arrival of recipient in anaesthetic room after porter sent to bring recipient to theatre.....	144
<b>3.10</b>	<b>Theatre factors and impact on cold ischaemia time.....</b>	<b>145</b>
3.10.1	Access to theatre .....	145
3.10.2	Timing of start of transplant surgery (knife to skin) in relation to arrival of recipient in anaesthetic room.....	147
3.10.3	Timing of start of transplant surgery (knife to skin) in relation to completion of crossmatching, recipient preparation and kidney delivery.....	148
3.10.4	Time interval between informing theatre and sending for recipient for transplant .....	149
3.10.5	Back table preparation time for donor kidney.....	150
3.10.6	Timing of knife to skin after back table preparation of donor kidney ....	151
3.10.7	Timing of removal of donor kidney from ice for anastomosis in recipient in relation to start of transplant surgery .....	152
3.10.8	Timing of reperfusion of kidney after removal of donor kidney from ice at transplantation surgery .....	153
<b>3.11</b>	<b>Univariate and multivariate analysis of significant factors contributing to cold ischaemic time .....</b>	<b>154</b>
3.11.1	Prospective pre-transplant crossmatch.....	156
3.11.2	Virtual crossmatch.....	159
<b>4</b>	<b>Discussion.....</b>	<b>162</b>
4.1	Summary .....	171

## Tables

Table 1.1 The Maastricht classification of donation after circulatory death.....	5
Table 1.2 DCD kidney sharing regions with designated transplant centres .....	12
Table 1.3 Kidney only transplant centres and multi-organ transplant centres.....	19
Table 1.4 List of H&I laboratories and the corresponding transplant centres.....	22
Table 3.1 General demographics .....	69
Table 3.2 Logistical variations in local transplant centre practices.....	71
Table 3.3 Overall cold ischaemia time .....	<b>Error! Bookmark not defined.</b>
Table 3.4 Cold ischaemia time in UK transplant centres in hours... <b>Error! Bookmark not defined.</b>	
Table 3.5 Cold ischaemia time in kidney only and multiorgan transplant centres....	75
Table 3.6 Cold ischaemia time for local/regional and imported kidney transplants..	77
Table 3.7 Cold ischaemia time for reallocated kidney transplants .....	79
Table 3.8 Cold ischaemia time in relation to type of kidney reallocation.....	81
Table 3.9 Cold ischaemia time for DBD and DCD donor kidney transplants .....	83
Table 3.10 Transplant centre variation in cold ischaemia time for DBD and DCD donor kidney transplants .....	86
Table 3.11 Timing of kidney offer and impact on cold ischaemia time.....	93
Table 3.12 Number transplants with pre-transplant crossmatch (pXM) and virtual crossmatch (vXM) .....	109
Table 3.13 Impact of type of crossmatch on cold ischaemia time.....	110
Table 3.14 Impact of crossmatch on cold ischaemia time for DBD and DCD kidney transplants.....	112
Table 3.15 H&I laboratory variation in crossmatching policy.....	116
Table 3.16 Cold ischaemia time for kidney transplants with pXM and vXM in each H&I laboratory .....	118
Table 3.17 Donor tissues for pXM.....	122
Table 3.18 Cold ischaemia time for kidney transplants with pre-retrieval peripheral blood and other donor tissues for pXM .....	124
Table 3.19 Cold ischaemia time for current or historic recipient serum sample used for pXM.....	131
Table 3.20 Recipient mode of travel to hospital for transplant .....	136
Table 3.21 Cold ischaemia time for transplants with or without recipient HD immediately before transplant .....	138

Table 3.22 Impact of recipient requirement for HD immediately pre-transplant with pXM and vXM on cold ischaemia time .....	140
Table 3.23 Cold ischaemia time in relation to access to theatre .....	146
Table 3.24 Univariate analysis for categorical factors contributing to cold ischaemia time in minutes .....	156
Table 3.25 Univariate analysis for continuous factors contributing to cold ischaemia time in minutes .....	157
Table 3.26 Multivariate analysis for factors contributing to cold ischaemia time....	158
Table 3.27 Univariate analysis for categorical factors contributing to cold ischaemia time in minutes .....	159
Table 3.28 Univariate analysis for continuous factors contributing to cold ischaemia time in minutes .....	160
Table 3.29 Multivariate analysis of factors contributing to cold ischaemia time .....	161

## Figures

Figure 1.1 Donor types.....	8
Figure 1.2 Number of deceased donors and transplants in the UK, 2008-2018 .....	9
Figure 1.3 Number of DBD and DCD donors in the UK, 2007-2017 .....	10
Figure 2.1 Summary of logistical factors that might contribute to cold ischaemic time, divided into 5 key areas.....	47
Figure 2.2 Transplants with pXM.....	62
Figure 2.3 Transplants with vXM.....	62
Figure 3.1 Overall cold ischaemia time .....	72
Figure 3.2 Transplant centre variation in median cold ischaemia time .....	73
Figure 3.3 Median cold ischaemia time in kidney only and multiorgan transplant centres.....	76
Figure 3.4 Median cold ischaemia time for local/regional and imported kidney transplants.....	78
Figure 3.5 Median cold ischaemia time for reallocated kidney transplants .....	80
Figure 3.6 Cold ischaemia time in relation to type of kidney reallocation.....	82
Figure 3.7 Cold ischaemia time for DBD and DCD donor kidney transplants .....	84
Figure 3.8 Mean cold ischaemia time for DBD and DCD donor kidney transplants in each transplant centre.....	87
Figure 3.9 Median cold ischaemia time for DBD and DCD donor kidney transplants in each transplant centre .....	88
Figure 3.10 Timing of kidney offer in relation to start of retrieval surgery in DBD and DCD donor kidney transplants .....	91
Figure 3.11 DBD and DCD kidney offer in relation to start of transplantation surgery (knife to skin) .....	92
Figure 3.12 Impact of timing of knife to skin in relation to kidney offer on cold ischaemia time .....	94
Figure 3.13 Impact of timing of DBD and DCD kidney offer in relation to retrieval surgery on cold ischaemia time.....	95
Figure 3.14 Timing of kidney in ice box in relation to in situ cold perfusion at retrieval surgery .....	96
Figure 3.15 Timing of kidney collection in relation to kidney put in ice box.....	97
Figure 3.16 Number of transplants in relation to distance between donor hospital and recipient transplant centre in miles.....	99

Figure 3.17 Impact of travel distance between donor hospital and recipient transplant centre on cold ischaemia time .....	100
Figure 3.18 Kidney collection to delivery time (kidney travel time) for DBD and DCD kidneys .....	102
Figure 3.19 Distance between donor hospital and recipient transplant centre for transport of DBD and DCD kidneys.....	103
Figure 3.20 Mode of transport of kidneys.....	105
Figure 3.21 Distance travelled by kidneys and the mode of transport .....	106
Figure 3.22 Kidney travel time and mode of transport .....	107
Figure 3.23 Impact of mode of transport of kidneys on cold ischaemia time .....	108
Figure 3.24 Impact of type of crossmatch on cold ischaemia time.....	110
Figure 3.25 Type of crossmatch for DBD and DCD kidney transplants .....	111
Figure 3.26 Impact of pXM and vXM on cold ischaemia time for DBD kidney transplants.....	113
Figure 3.27 Impact of pXM and vXM on cold ischaemia time for DCD kidney transplants.....	114
Figure 3.28 H&I laboratory variation in crossmatching policy .....	115
Figure 3.29 Impact of H&I laboratory variation in crossmatching policy on cold ischaemia time .....	117
Figure 3.30 Median cold ischaemia time for H&I laboratories that perform vXM in more than 50% or less than 50% of kidney transplants .....	120
Figure 3.31 Distribution of time interval between in situ cold perfusion and decision to proceed to transplant with a vXM .....	121
Figure 3.32 Impact of type of donor tissue used for pXM on cold ischaemia time .	123
Figure 3.33 Impact of pre-retrieval peripheral blood and other donor tissue used for pXM on cold ischaemia time .....	125
Figure 3.34 Donor tissues used for pXM in DBD and DCD kidney transplants.....	126
Figure 3.35 Impact of donor pre-retrieval peripheral blood versus other donor tissue used for pXM on cold ischaemia time in DCD kidney transplants.....	127
Figure 3.36 Impact of donor pre-retrieval peripheral blood versus other donor tissue used for pXM on cold ischaemia time in DBD kidney transplants .....	128
Figure 3.37 H&I laboratory variation in the use of stored (historic) and 'at transplant' (current) recipient sample for pXM .....	130
Figure 3.38 Impact of historic (stored) and current ('at transplant') recipient serum sample for pXM on cold ischaemia time.....	132



Figure 3.39 Impact of historic and current recipient sample for pXM on cold ischaemia time in DBD and DCD kidney transplants .....	133
Figure 3.40 Distribution of pXM time .....	134
Figure 3.41 Distribution of time interval between in situ cold perfusion and reporting of pXM result .....	135
Figure 3.42 Impact of recipient mode of travel on cold ischaemia time .....	137
Figure 3.43 Impact of recipient requirement for HD immediately pre-transplant on cold ischaemia time .....	139
Figure 3.44 Impact of recipient requirement for HD immediately pre-transplant in pXM and vXM group on cold ischaemia time .....	141
Figure 3.45 Distribution of time interval between offer accepted and recipient contacted for kidney transplantation.....	142
Figure 3.46 Distribution of time interval between recipient contacted and arrived for transplant.....	143
Figure 3.47 Distribution of time interval between recipient sent for and arrived in anaesthetic room .....	144
Figure 3.48 Impact of theatre access on cold ischaemia time .....	146
Figure 3.49 Distribution of recipient time in anaesthetic room .....	147
Figure 3.50 Distribution of time interval between completion of all preparation for transplant and knife to skin.....	148
Figure 3.51 Distribution of time interval between informing theatre and sending for recipient for surgery.....	149
Figure 3.52 Distribution of back table preparation time .....	150
Figure 3.53 Distribution of time interval between completion of back table preparation and knife to skin .....	151
Figure 3.54 Distribution of time interval between knife to skin and donor kidney removal from ice for anastomosis into recipient .....	152
Figure 3.55 Distribution of time interval between removal of donor kidney from ice and re-establishment of kidney perfusion.....	153
Figure 3.56 Distribution of cold ischaemia time in kidney transplants with pXM and vXM .....	155
Figure 4.1 Logistical areas for possible intervention to reduce CIT .....	169

<b>Bibliography .....</b>	<b>187</b>
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## **Appendix**

Appendix 1: Publication

Appendix 2: South East Scotland Research Ethics Service approval

Appendix 3: Questionnaire for specialist nurse for organ donation (donation information)

Appendix 4: Questionnaire for Histocompatibility and Immunogenetics staff (HLA crossmatching information)

Appendix 5: Questionnaire for recipient coordinator (recipient and transplant information)

Appendix 6: Questionnaire for transport personnel (kidney transport information)

Appendix 7: Questionnaire for transplant centre practices

Appendix 8: Newsletter 1

Appendix 9: Newsletter 2

# **1 Introduction**

## **1.1 History of renal transplantation**

Renal transplantation has evolved over the last century as one of the most significant developments in the history of medicine. In the early twentieth century French surgeon Alexis Carrel achieved technical success by developing and perfecting the method of vascular anastomosis and vessel reconstruction (Linden, 2009). In 1945, Peter Medawar identified rejection response and demonstrated that allograft rejection was an immunological process (Linden, 2009, Dyer and Johnson, 2004).

The first recorded human organ transplant from deceased donor was performed by Russian surgeon Voronoy in 1936 (Dyer and Johnson, 2004). The first successful human organ transplant was a kidney from monozygotic twin donor at The Peter Bent Brigham Hospital in Boston on December 23<sup>rd</sup>, 1954 by Joseph Murray and John Merrill. Hume transplanted kidney from a deceased donor successfully in 1953 (Dyer and Johnson, 2004).

In the United Kingdom (UK), Sir Michael Woodruff and his team successfully transplanted kidney for the first time from an identical twin at The Royal Infirmary of Edinburgh on October 30<sup>th</sup>, 1960 (Kessaris et al., 2008). A kidney transplant from a deceased donor was first performed in the UK in 1967 (NHS, 2018)

The legal guidelines for brain-stem death were first defined in 1968 by the Ad Hoc Committee of the Harvard Medical School, increasing access to organs for transplantation. This was later refined in 1981. In 2006, deceased donor organ transplantation following donation after cardiac death (DCD) was introduced and became acceptable as a means to increase donor organs for transplantation (Linden, 2009).

In the mid 1960s, it was demonstrated that transplanting kidney to a recipient previously exposed to alloantigens led to hyperacute rejection of the transplanted organ. This was detected by a crossmatch test between recipient serum and donor lymphocytes. This pre-transplant crossmatch test (pXM) was further developed and established by Terasaki in 1965. It has since been universally used and has been instrumental in avoiding hyperacute rejection by excluding donor-specific sensitisation prior to transplantation. Terasaki also developed a microtechnique for HLA typing and antibody screening (Dyer and Johnson, 2004, Murray et al., 1976).

The development and use of effective immunosuppression for transplantation has evolved from prophylactic total body irradiation in the 1950s to modern and less toxic chemical immunosuppressive agents (Murray et al., 1976). The use of cyclosporine in 1981 was a landmark in the development of immunosuppression in transplant (Dyer and Johnson, 2004).

There has been major progress in both surgical techniques and immunosuppressive therapy in transplantation over the last several decades. The quest to minimise organ

damage to improve transplant outcomes continues. Belzer in 1967 demonstrated that kidneys could safely be stored up to 72 hours by perfusion with plasma at 10 degree Celsius continuously. In 1969, Collins introduced storage in ice simplifying the process by advances in organ preservation techniques (Dyer and Johnson, 2004).

## **1.2 Renal transplant versus dialysis**

Renal transplantation remains the optimal treatment for the majority of patients with end stage renal failure. The development of renal transplantation has been facilitated by an increasing awareness of organ donation, advances in organ retrieval, allocation, preservation and surgical technique, and significant progress in immunosuppression and management of infection post transplant (Neipp et al., 2009, Linden, 2009).

Renal transplantation is shown to increase quality of life and reduce comorbidities associated with dialysis in several studies (Neipp et al., 2009, Maglakelidze et al., 2011, Sayin et al., 2007). It is also shown to be associated with longer survival in elderly recipients (Bayat et al., 2010, Wolfe et al., 1999). A study comparing cost-effectiveness between renal transplantation and dialysis has shown significantly higher cost in dialysis patients. It also showed significant physical and psychological advantage and better quality of life in the transplanted patients (Perovic and Jankovic, 2009, Sayin et al., 2007). According to NHS Blood and Transplant (NHSBT), the strategic health authority that oversees transplantation in the UK, the cost-benefit of kidney transplantation over a ten-year period in the UK compared to

dialysis is a quarter of million pounds (NHSBT, 2018c). A study comparing the mortality of patients on dialysis awaiting transplantation with those who received first deceased donor kidney transplant showed 48% to 82% lower long-term mortality rate in the latter (Wolfe et al., 1999).

A systematic review of 110 studies comparing clinical outcomes between kidney transplantation and dialysis showed considerable advantage of transplantation over dialysis, with significantly reduced mortality and risk of cardiovascular events and better quality of life. This was also true despite increase in age and comorbidities with the benefits appearing to increase over time (Tonelli et al., 2011).

### **1.3 Deceased organ donation**

Kidney transplantation can be broadly divided into two categories; living donor (LD) transplant and deceased donor (DD) transplant, depending on whether the kidney was retrieved from a living person or from a deceased donor.

In the UK there are two types of deceased donors who are eligible for organ donation. Donors after brainstem death (DBD) are those for whom death was confirmed following neurological tests and who had no medical contraindications for solid organ donation (NHSBT, 2018a). Donors after circulatory death (DCD) are those for whom death was anticipated within four hours after withdrawal of treatment and who had no medical contraindications for solid organ donation. The clinical categories of DCD include four subgroups described by the Maastricht

Classification depending on the circumstances and manner of circulatory arrest  
(NHSBT, 2018b). (Table 1.1)

**Table 1.1 The Maastricht classification of donation after circulatory death(NHSBT, 2018b)**

Category	Type	Circumstances	Typical Location
1	Uncontrolled	Dead on arrival	Emergency Department
2	Uncontrolled	Unsuccessful resuscitation	Emergency Department
3	Controlled	Cardiac arrest follows planned withdrawal of life sustaining treatments	Intensive Care Unit
4	Either	Cardiac arrest in a patient who is brain dead	Intensive Care Unit

The two principal types of DCD are controlled and uncontrolled. Organ retrieval following unexpected and irreversible circulatory arrest is referred to as uncontrolled DCD and that following planned withdrawal of life sustaining treatment considered to be of no overall benefit to the patient is controlled DCD. Uncontrolled DCD organ retrieval is currently inactive in the UK (NHSBT, 2018b).

The contribution of DCD organs to overall deceased donor transplantation varies in different countries. Some countries including Sweden, New Zealand and Norway do not have a DCD programme for transplantation. Countries that do have DCD

programmes include the UK, the Netherlands, Australia, Spain and France. In the UK, there has been a significant increase in the number of DCDs year on year, over the last decade, from 200 donors in 2007-2008 to 584 in 2016-2017 contributing to 41% of deceased organ donation (NHSBT, 2018b).

The major challenge facing the transplant community is the shortage of organs for donation as demand outstrips supply (Rosendale et al., 2002, Audard et al., 2008, De Paolis et al., 2016, Solomon, 2011). The patients awaiting transplant are increasingly at risk of deterioration and death without a transplant. To meet the ever-increasing demand there have been significant changes in practice over the last decade with increasing use of organs that would previously have been considered unsuitable for transplant (Ojo et al., 2001, Port et al., 2002). These donors are referred to as extended/expanded criteria donors (ECD) (Metzger et al., 2003). (Figures 1.2, 1.3)

The United Network of Organ sharing (UNOS) came up with a policy to define the ECD by donor characteristics that are associated with a 70% greater risk of kidney graft failure when compared to a standard criteria donor (SCD). The aim was to maximise the retrieval and use of ECD kidneys by providing mechanisms to minimise ECD cold storage time and to expedite ECD kidney allocation (Audard et al., 2008).



ECD kidney is defined as –

- All donors equal to or above 60 years of age.
- Donors equal to or above 50 years of age and less than 60 years of age with any two or more of the following risk factors:

CVA as cause of death

Hypertension

Creatinine >1.5mg/dl

The types of donors for organs are – (Figure 1.1)

LD – living donor

DD – deceased donor

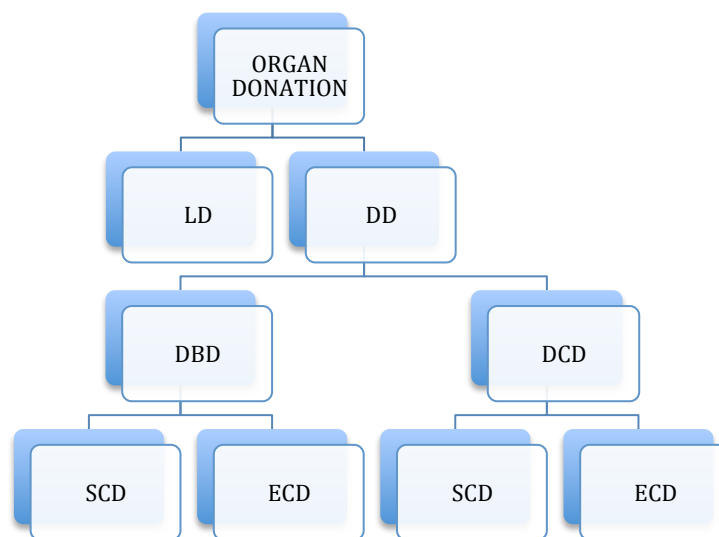
DBD – donation after brain death donor

DCD – donation after circulatory death donor

SCD – standard criteria donor

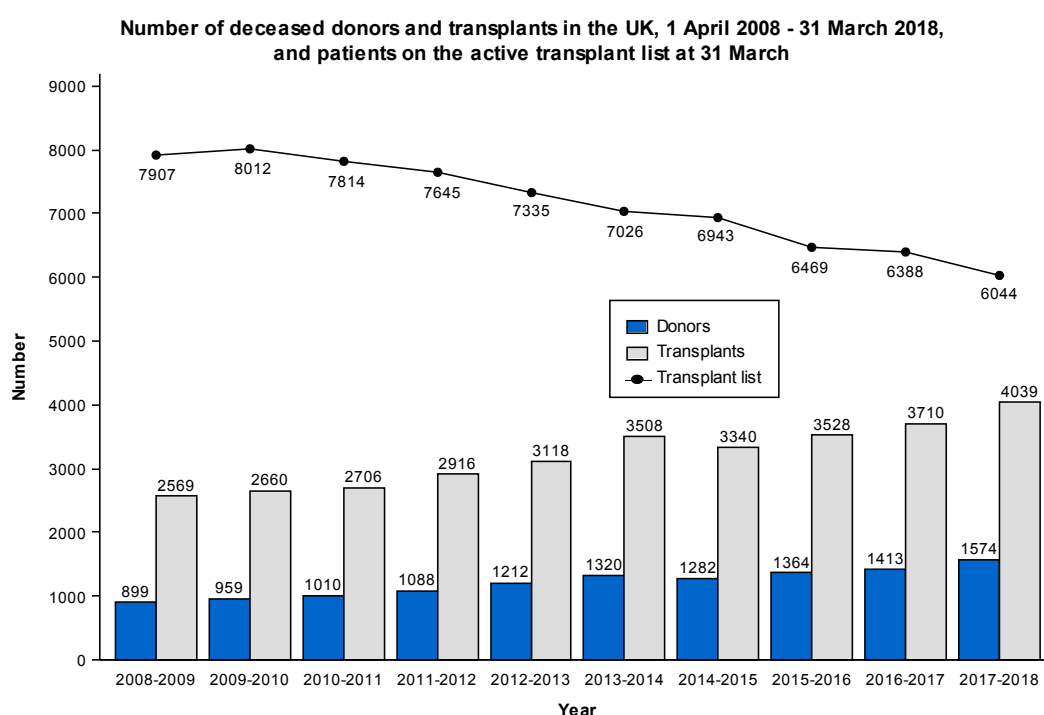
ECD – extended criteria donor

**Figure 1.1 Donor types**



**Figure 1.2 Number of deceased donors and transplants in the UK, 2008-2018**

(NHSBT, 2018e)

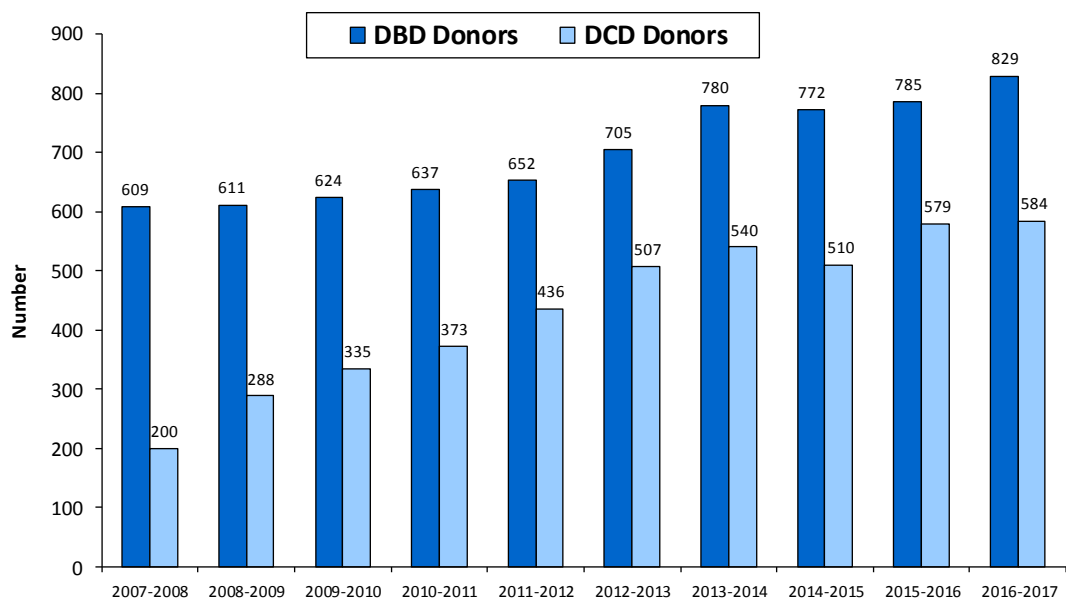


Source: Transplant activity in the UK, 2017-2018, NHS Blood and Transplant

Source: Transplant activity in the UK, 2017-2018, NHS Blood and Transplant

**Figure 1.3 Number of DBD and DCD donors in the UK, 2007-2017**

(NHSBT, 2018e)



Source: Transplant activity in the UK, 2017-2018, NHS Blood and Transplant

A study comparing the mortality rate of ECD kidneys with that of SCD and with relevant reference group of similar wait-listed dialysis patients showed that ECD kidney transplantation is associated with a significant survival benefit over dialysis patients with an increased life expectancy by 5.1 years but lower graft survival of 53% and patient survival of 74% compared to 67% and 80%, respectively, for SCD kidneys (Ojo et al., 2001).

It is well established that younger recipients of kidneys from younger donors have superior survival outcome. In an Australian cohort study, it has been shown that survival outcome is poorer when ECD kidneys are transplanted in younger recipients compared with those with standard criteria donor (SCD) kidneys (Ma et al., 2016). A single centre study from Germany also demonstrated that kidneys from old donors fared significantly worse in young recipients and significantly better in old recipients (Waiser et al., 2000).

#### **1.4 Deceased donor kidney allocation policy**

In the UK kidneys from DBD donors are allocated through a National Allocation Scheme managed by NHSBT. Kidneys from DCD donors are allocated regionally through a National Sharing Scheme where one kidney is offered preferentially to the local transplant centre and the second of the pair is shared regionally within four defined regions. Each donor hospital is allocated to one of the four DCD kidney sharing regions and offers are restricted to recipients of transplant centres within the region for donor hospital (NHSBT, 2017). (Table 1.2)

**Table 1.2 DCD kidney sharing regions with designated transplant centres**

(NHSBT, 2017)

<b>North</b>	<b>Midlands</b>	<b>South West</b>	<b>London</b>
Edinburgh	Birmingham	Bristol	GOSH
Glasgow	Cambridge	Cardiff	Guy's
Leeds	Coventry	Oxford	The Royal Free
Liverpool	Leicester	Plymouth	The Royal London
Manchester	Nottingham	Portsmouth	St George's
Newcastle	Sheffield		WLRTC
	Belfast		

Since completion of this study, there has been a change in allocation scheme for kidneys from DCD donors; on 3 September 2014, a new National DCD Kidney Allocation Scheme was introduced. One kidney from all DCD donors are now allocated to local centre and second kidney from donors between 5 and 59 years are allocated within the 4 regional centres (NHSBT, 2015) (Table 1.2).

## **1.5 Principles of deceased donor kidney allocation scheme**

A new National Allocation Scheme for DBD kidneys was introduced in the UK in 2006 (Johnson et al., 2010a). When the NHSBT is notified of an organ donor, the most suitable recipient on the waiting list for deceased donor kidney transplant is prioritised for transplant through points-based and evidence-based computer algorithm.

The five tiers are (NHSBT, 2017, Johnson et al., 2010a):

A: 000 mismatched paediatric patients – highly sensitised or HLA-DR homozygous (complete matches for children – difficult to match patients)

B: 000 mismatched paediatric patients – others (all except those in Tier A) (complete matches for children – others)

C: 000 mismatched adult patients – highly sensitised or HLA-DR homozygous (complete matches for adults – difficult to match patients)

D: 000 mismatched adult patients – others (all except those in Tier C) (others)

Favourably matched paediatric patients (100, 010, 110 mismatches) (well matched children)

E: All other eligible patients (adults and children)

Within Tiers C, D and E patients are prioritised based on the following points-based criteria:

- Waiting time
- HLA match and age combined
- Donor-recipient age difference
- Location of patient relative to donor
- HLA-DR homozygosity
- HLA-B homozygosity
- Blood group match

This new allocation scheme which is based on evidence base outcomes has been hailed as an important contribution to allocation of DBD kidneys in the UK in a follow up commentary (Morris and Monaco, 2010).

## **1.6 Reallocation of kidneys**

When an accepted kidney cannot subsequently be utilised for the selected recipient it is reallocated according to NHSBT policy. It is offered to the next patient on the priority list if the kidney has not yet been dispatched to the first transplant centre. If it is already dispatched to the first transplant centre, it is offered locally, regionally or nationally as appropriate (NHSBT, 2017).



## **1.7 Logistics of kidney donation and transplantation in the United Kingdom**

### **1.7.1 National Health Service Blood and Transplant (NHSBT) and Organ Donation and Transplantation (ODT)**

Deceased donor kidney is the most commonly transplanted organ in the UK (NHSBT, 2017). The health authority NHSBT and its directorate Organ Donation and Transplantation are responsible for coordinating and implementing transplant activities across the UK. The ODT maintains the DD kidney transplant waiting list and receives notification of potential donors. It mobilises Specialist Nurses for Organ Donation (SN-OD) to coordinate the process of donation, manages matching of the organs with recipients on the waiting list, offers the organs to suitable recipients and directs National Organ Retrieval Service. Its responsibility includes transplant outcome data collection for the National Transplant Database (NHSBT, 2018d) .

### **1.7.2 Specialist nurses for organ donation (SN-OD)**

These specialist nurses are responsible for all aspects of the process of donation including notification to the Duty Office of potential donors and preparation and facilitation of the donation process.

There are 12 regional donor transplant coordinator teams across the UK supporting their regional transplant centres –

1. Eastern Region, Cambridge
2. London Region, London
3. Midlands Region, Birmingham
4. Northern Ireland Region, Belfast
5. North West Region, Liverpool
6. Northern Region, Newcastle
7. Scotland Region, Falkirk
8. South Central Region, Oxford
9. South East Region, West Sussex
10. South Wales Region, Cardiff
11. South West Region, Exeter
12. Yorkshire Region, Leeds

### **1.7.3 Kidney transplant centres**

There are 24 kidney transplant centres in the UK. Some of them are kidney only transplant units and the others transplant multiple organs including kidneys. These are –

1. Belfast, City Hospital
2. Birmingham, Queen Elizabeth Hospital
3. Bristol, Southmead Hospital
4. Cambridge, Addenbrooke's Hospital
5. Cardiff, University Hospital of Wales
6. Coventry, University Hospital
7. Edinburgh, Royal Infirmary
8. Glasgow, Western Infirmary
9. Leeds, St James's University Hospital
10. Leicester, General Hospital
11. Liverpool, Royal Liverpool University Hospital
12. London, Great Ormond Street Hospital
13. London, Guy's Hospital
14. London, St George's Hospital
15. London, The Royal Free Hospital
16. London, The Royal London Hospital
17. London, West London Renal and Transplant Centre (Hammersmith Hospital)
18. Manchester, Royal Infirmary

19. Newcastle, Freeman Hospital
20. Nottingham, City Hospital
21. Oxford, Churchill Hospital
22. Plymouth, Derriford Hospital
23. Portsmouth, Queen Alexandra Hospital
24. Sheffield, Northern General Hospital

City Hospital, Belfast was not included in the study. Great Ormond Street Hospital and Guy's Hospitals were considered as one unit. Eleven of the 22 transplant centres included were kidney only transplant centres and the other 11 were multi-organ transplant centres. (Table 1.3)

**Table 1.3 Kidney only transplant centres and multi-organ transplant centres**

<b>Kidney Only Transplant Centres</b>	<b>Multi-organ Transplant Centres</b>
Coventry, University Hospital Coventry and Warwick	Birmingham, Queen Elizabeth Hospital
Glasgow, Western Infirmary	Cambridge, Addenbrooke's Hospital
Leicester, Leicester General Hospital	Cardiff, University Hospital of Wales
Liverpool, Royal Liverpool University Hospital	Edinburgh, Royal Infirmary
London, St George's Hospital	Leeds, St James's University Hospital
London, The Royal London Hospital	London, Guy's Hospital
Nottingham, City Hospital	London, The Royal Free Hospital
Plymouth, Derriford Hospital	Manchester, Manchester Royal Infirmary
Bristol, Southmead Hospital	Newcastle, Freeman Hospital
Sheffield, Northern General Hospital	Oxford, Churchill Hospital
Portsmouth, Queen Alexandra Hospital	London, West London Hammersmith Hospital

#### **1.7.4 Histocompatibility and Immunogenetics laboratories**

There are 20 Histocompatibility and Immunogenetics (H&I) laboratories in the UK supporting regional transplant centres and these are responsible for tissue typing (TT) and crossmatching of the donor and recipient tissues and serum to establish HLA typing and compatibility of the donor organ and the recipient for transplantation. The laboratories are –

1. Birmingham, NHSBT
2. Bristol, Southmead Hospital
3. Cambridge, Addenbrooke's Hospital
4. Edinburgh, SNBTS
5. Glasgow, Gartnavel Hospital
6. Leeds, St James's University Hospital
7. Leicester, General Hospital
8. Liverpool, Royal Liverpool University Hospital
9. London, Guy's Hospital
10. London, Royal Free Hospital
11. London, Royal London Hospital
12. London, Hammersmith Hospital
13. London, NHSBT Tooting
14. Manchester, Royal Infirmary
15. Newcastle, NHSBT
16. Northern Ireland, Blood Transfusion Service

17. Oxford, Churchill Hospital
18. Plymouth, Derriford Hospital
19. Sheffield, NHSBT
20. Wales, Welsh Blood Service

Each H&I laboratory supports transplants in a single transplant centre with the exception of 4 laboratories. NHSBT Birmingham supports Birmingham and Coventry and Guy's Hospital H&I laboratory supports Guy's Hospital, Great Ormond Street Hospital and part of St George's Hospital transplants. NHSBT Tooting supports Portsmouth Hospital and part of St George's Hospital transplants and NHSBT Sheffield supports Sheffield and Nottingham transplant centres. (Table 1.4)

**Table 1.4 List of H&I laboratories and the corresponding transplant centres**

<b>H&amp;I laboratories</b>	<b>Transplant centres</b>
Birmingham, NHSBT	Birmingham
	Coventry
Bristol, Southmead Hospital	Bristol
Cambridge, Addenbrooke's Hospital	Cambridge
Edinburgh, SNBTS	Edinburgh
Glasgow, Gartnavel Hospital	Glasgow
Leeds, St James's University Hospital	Leeds
Leicester, General Hospital	Leicester
Liverpool, Royal Liverpool University Hospital	Liverpool
London – Guy's Hospital	London – Guy's
	London – GOSH
	London – St George's
London – NHSBT Tooting	Portsmouth
Manchester, Royal Infirmary	Manchester
Newcastle, NHSBT	Newcastle
Northern Ireland, Blood Transfusion Service	Belfast
Oxford, Churchill Hospital	Oxford
Plymouth, Derriford Hospital	Plymouth
Sheffield, NHSBT	Sheffield
	Nottingham
Wales, Welsh Blood Service	Wales



### **1.7.5 Transplant centre teams**

Each transplant unit consists of a multidisciplinary team of specialists including Recipient Coordinators, Transplant Surgeons and Specialist Registrars, Nephrologists, H&I Staff and, Ward and Theatre Staff. In majority of the transplant units, deceased donor Recipient Coordinators (RC) are responsible for organisation, support, guidance and preparation of potential recipients in the process of kidney transplantation.

### **1.8 Potential donors**

When a potential donor is identified, SN-ODs notify ODT and arrange collection and dispatch of donor blood sample to local H&I laboratory for HLA typing. The result of the HLA typing is then faxed to the ODT who undertake a computerised match run against the wait-listed potential recipients using a complex algorithm and this provides a shortlist of potential recipients.

### **1.9 Establishing donor and recipient compatibility**

HLA matching is performed to determine the degree of histocompatibility between a donor and a recipient prior to transplant to avoid hyper-acute or accelerated graft rejection.

### **1.9.1 Determining donor and potential recipient HLA type**

The human leucocyte antigen (HLA) molecules are membrane bound glycoproteins that play a central role in antigen presentation and recognition in immune response regulation (Howell et al., 2010). The genes coded for HLA molecules are located on the short arm of chromosome 6 which is also known as major histocompatibility complex (MHC). HLA class I and class II genes are involved in the transplant immune response. Donors and potential recipients, before being wait-listed for transplantation, are HLA typed for class I (HLA-A, -B and -C) and class II (HLA-DR, -DQ) genes by DNA based technology (Dyer, 2008). Donor HLA type is determined locally using donor peripheral blood obtained prior to organ retrieval (Taylor et al., 2000).

There are two methods for determining the HLA type: serological, which is based on detection of genetic variation in the expressed HLA molecules and DNA based technique (Howell et al., 2010). Typing with the DNA-based method is more accurate than serological method; sample testing can be repeated when required as DNA is easily stored and it does not require live lymphocytes (Cecka, 2009).

### **1.9.2 Potential recipient HLA antibody screening**

All patients on the transplant waiting list are regularly screened for HLA alloantibodies to identify any unacceptable donor HLA antigens to which anti-donor antibodies may be present in the sera and hence avoid positive XM and unnecessary

transport of kidneys. Equally, in absence of HLA specific antibodies, transplantation can safely proceed without a prospective crossmatch (XM), also called virtual crossmatch (vXM). Patient samples are screened on a 3 monthly basis for routine antibody monitoring according to BTS guidelines as their sensitisation may vary over time. Samples are also screened for potential sensitisation between two and four weeks following transfusion, pregnancy or transplantation (BTS-BSHI, 2015, Taylor et al., 2010).

There are various methods for HLA specific antibody detection and characterisation. Cell based assays such as complement dependent cytotoxicity (CDC) use lymphocyte panels of HLAs representing the donor population (Taylor et al., 2010). Solid-phase immunoassay (SPI) does not require viable lymphocytes and complement and also provides greater sensitivity than CDC assay of which Luminex assay is considered gold standard (Howell et al., 2010, Tait et al., 2013, BTS-BSHI, 2015). CDC assay is still used for screening and crossmatching in supplement to Luminex assay (BTS-BSHI, 2015, Tait et al., 2013).

### **1.10 Immediate pre-transplant donor- recipient compatibility assessment**

Crossmatching test is performed prior to transplant to identify unacceptable antibodies in the recipient serum that are reactive with donor lymphocytes and, hence, to avoid hyperacute rejection.

### **1.10.1 Pre-transplant laboratory crossmatch test**

Pre-transplant crossmatching (pXM) is performed to establish compatibility between the donor and potential recipient using two methods; complement dependent cytotoxicity (CDC-XM) and flow cytometry (FC-XM). These tests are used to confirm the presence or absence of donor specific antibodies (DSA) in the recipient serum against the donor lymphocytes (Howell et al., 2010, Cecka, 2009). Crossmatch test can be performed with historical recipient sample, without the need of waiting for a current sample to be available, if there is no recent history of sensitising events (Cecka, 2009). Donor lymphocytes are isolated from pre-retrieval peripheral blood that was obtained for HLA typing, or from spleen and/or lymph nodes following organ retrieval (BTS-BSHI, 2015). It takes between 4 and 6 hours to perform the pXM (Taylor et al., 2010).

### **1.10.2 Virtual crossmatch**

In some carefully selected recipients, kidney transplantation can safely proceed without the need for a pre-transplant crossmatch test (Taylor et al., 2000, Dyer and Taylor, 2000, Taylor et al., 2010, Tambur et al., 2009). A negative crossmatch between donor and recipient can be predicted if the recipient has clearly defined stable HLA-specific antibodies, negative screening history and no recent history of sensitising events which is described as virtual crossmatch (vXM) (Cecka, 2009, Taylor et al., 2010, Dyer and Taylor, 2000).

A virtual crossmatch policy in deceased donor kidney transplants was first introduced in the UK in Cambridge two decades ago (Taylor et al., 2000). In 2010, they published a large ten-year prospective study demonstrating safe application of vXM policy routinely on recipients with low sensitisation in deceased donor kidney transplantation (Taylor et al., 2010). The study included a total of 606 deceased donor kidney transplants, 42% of which went ahead with a vXM. A retrospective XM was performed in each case to confirm the negative prediction. More recently, a Spanish study examining the results of implementation of a national priority allocation system based on vXM for highly sensitised patients found that it was highly effective in increasing their access to transplantation (Valentin et al., 2016).

The results of the final crossmatch test are carefully reviewed by histocompatibility expert and discussed with the transplanting surgeon or nephrologist to review any relevant risk factors before proceeding with transplant (Dyer and Taylor, 2000).

At the time of this study, all UK H&I units with the exception of H&I units at Hammersmith and Newcastle had a vXM policy for deceased donor kidney transplants.

### **1.11 Ischaemia-reperfusion injury**

Ischaemia-reperfusion injury is inevitable in deceased donor kidney transplantation as a consequence of interruption and subsequent re-establishment of blood flow to the organ and influences clinical outcomes such as early graft rejection (Salvadori et al., 2015). Renal ischaemia occurs early in the retrieval process when blood flow to kidney is interrupted when the aorta is clamped. This leads to initial short period of severe hypoxic tissue injury that initiates a series of events at the cellular and molecular level leading to micro-vascular dysfunction (van der Vliet and Warle, 2013, Salvadori et al., 2015). The ischaemic injury is further compounded by a longer period of hypothermic perfusion and storage leading to further cellular dysfunction (Salvadori et al., 2015, Zhao et al., 2018, Pratschke et al., 2008). Revascularisation of the kidney at transplantation restores the blood supply and oxygenation to the tissues but, paradoxically, triggers a complex sequence of events associated with apoptosis, endothelial injury and innate and adaptive immune response, thus aggravating the damage and leading to structural impairment at cellular level and cell death (Pratschke et al., 2008, Salvadori et al., 2015). There is a strong association between severity of early graft failure and severity of ischaemia-reperfusion injury (Zhao et al., 2018).

## 1.12 Delayed graft function

Delayed graft function (DGF) is an early clinical manifestation of a transplanted kidney when it fails to function in the immediate post-transplant period due to ischaemia-reperfusion and immunological injuries sustained in the process of retrieval and transplantation (Yarlagadda et al., 2008, Ditonno et al., 2013, Moreso et al., 1999, Jung et al., 2010). There is no standardised definition of delayed graft function (DGF) in the literature. The definition of DGF is either dialysis based or creatinine based or a combination of dialysis, creatinine and urine output. Some of the studies have defined it as failure of serum creatinine to fall by less than 10% a day for three consecutive days while others define it as biopsy proven acute tubular necrosis (ATN) or, serum creatinine decreasing by less than 1.1mg/dL in the first five days. A systematic review of definition of DGF identified 18 unique variations in the definition and diagnosis of DGF. However, the majority of the studies have defined DGF as requirement for dialysis in the first week post-transplant (Yarlagadda et al., 2008, Rosenthal et al., 1991, Perico et al., 2004, Ditonno et al., 2013, Daly et al., 2005, Jung et al., 2010).

There is wide variation in the incidence of DGF ranging from 5% to 50% in deceased donor kidney transplantation (Ojo et al., 1997, Yarlagadda et al., 2008, Perico et al., 2004). This has not improved despite major advances in transplantation (Yarlagadda et al., 2008, Chapal et al., 2014, Sharif and Borrows, 2013). DGF is known to be associated with poorer outcomes including acute and chronic graft rejection, chronic allograft nephropathy, decreased graft survival and graft loss

(Yarlagadda et al., 2008, Yarlagadda et al., 2009, Troppmann et al., 1995). This leads to considerable morbidity, requirement of additional immunosuppression, radiological studies and biopsies leading to prolonged hospital stay and potential return to dialysis, which have considerable financial implications and poorer long-term survival (Yarlagadda et al., 2008, Ojo et al., 1997, Rosenthal et al., 1991, Ditunno et al., 2013, Freedland, 1999, Cecka, 2001, Marcen et al., 1998).

Results of studies evaluating the impact of DGF on kidney transplant outcomes are controversial with some studies indicating minimal or no impact on graft survival and others associating it with poor long-term graft survival (Ojo et al., 1997). In a large study, Ojo et al found that DGF was significantly associated with reduction in short and long-term graft survival. It not only exacerbated the effect on allograft survival but also had greater impact than HLA matching on post transplant outcomes (Ojo et al., 1997). Another study by Butala et al found strong evidence suggestive of causal effect of DGF on graft failure and mortality at 1 and 5 years (Butala et al., 2013). A meta-analysis by Yarlagadda et al showed 41% more risk of graft loss at 3.2 years and 38% relative increased risk of acute rejection compared to patients without DGF (Yarlagadda et al., 2009).

In the current scenario of organ shortage and increasing use of ECD kidneys, it is important that we adopt all possible measures to decrease the incidence of DGF to mitigate its short and long term impact on transplanted kidneys (Yarlagadda et al., 2009, Chapal et al., 2014, Perico et al., 2004, Moreso et al., 1999). Minimising



ischaemic injury by reducing cold storage time and improving organ preservation pre-transplant are important factors in reducing the risk of DGF (Gill et al., 2014).

### **1.13 Kidney preservation (Machine perfusion versus cold storage)**

Preservation of donor kidneys for transplant involves either static cold storage or dynamic machine perfusion (Hameed et al., 2016). Although machine perfusion was used several decades ago in conjunction with static cold storage, there has been resurgence in their use in the last decade especially because of increasing use of DCD and ECD kidneys for transplantation (Hameed et al., 2017, Yuan et al., 2010). Preservation of organs with machine perfusion is still evolving and cold storage remains the principal method of kidney preservation prior to deceased donor kidney transplant (Hameed et al., 2016, Lam et al., 2013). There are different techniques used for machine perfusion, namely, hypothermic machine perfusion, oxygenated machine perfusion and normothermic machine perfusion (Jochmans et al., 2015). Factors such as ideal perfusate solution, optimum temperature and timing for machine perfusion are currently undetermined (Kaths et al., 2018, De Deken et al., 2016). It is apparent that kidneys with different baseline risks require different preservation techniques (Jochmans et al., 2016).

Machine perfusion in transplantation is still evolving and remains widely debated (Jochmans et al., 2016, Jochmans et al., 2017). An international randomised controlled trial (RCT) comparing hypothermic machine perfusion with cold storage of deceased donor kidneys showed reduced risk of DGF and better 1-year graft

survival after machine perfusion. DBD kidneys showed better survival at 3 years post-transplant, especially in ECDs but DCD kidneys showed no graft survival benefit after machine perfusion compared to cold storage (Moers et al., 2009, Moers et al., 2012). A large registry data analysis examining pulsatile machine perfusion and DGF found reduced risk of DGF with machine perfusion in all deceased donor kidneys regardless of the length of cold storage (Gill et al., 2014). However, other studies have not shown consistency in graft survival with machine perfusion (Sandal et al., 2018). A systematic analysis of seven RCTs showed no effect of machine perfusion on primary non-function (PNF), graft loss and patient death at 1-year for DBD and DCD kidneys despite significant reduction in DGF (Lam et al., 2013). A recent study of large registry data analysis showed no benefit of machine perfusion in kidney transplant outcomes beyond 1 year. It questions the use of machine perfusion in deceased donor kidney transplant as it showed no long-term benefit especially in ECD and DBD kidneys (Sandal et al., 2018). Another multicentre RCT from the UK comparing cold machine perfusion with static cold storage of DCD kidneys showed no difference in the incidence of DGF. Also, there was no advantage of machine perfusion over cold storage for DCD kidneys (Watson et al., 2010).

## **1.14 Cold ischaemia time**

Cold ischaemia time (CIT) is defined as the time interval between in situ cold perfusion of the kidney at donor operation and removal from ice for anastomosis at recipient operation (Sweny, 2017, van der Vliet and Warle, 2013, van der Vliet et al., 2011).

A period of CIT is unavoidable in the process of deceased donor kidney transplantation. It requires the retrieved kidneys to be stored in ice to reduce the metabolic demands until they can be transplanted. This allows the kidneys to be shipped to a different centre for transplantation to best-matched recipients in accordance with the national allocation policy.

### **1.14.1 Why is Cold Ischaemia Time important?**

Cold ischaemia time is one of the most important factors that influence outcomes after deceased donor kidney transplants. It is known to be the principle predictor of DGF (Cecka, 2001, Ojo et al., 1997).

A study analysing factors influencing outcome after DBD kidney transplants in the UK to inform the new Kidney Allocation Scheme identified CIT to have a strong influence on short-term graft outcome with a 4% increase in risk of graft failure for each additional hour of CIT beyond 21 hours. CIT was prolonged by reallocation and exchanges of kidneys between distant transplant centres. CIT increased by 30

minutes on average when a kidney was declined by the centre to which it was initially offered. When a kidney was accepted by a centre for a patient but was subsequently reallocated and transplanted in another recipient at the same centre, CIT increased by an average of 7 hours. CIT increased by 2 hours in the case of long distance kidney exchanges between different UK centres (Johnson et al., 2010b).

A UK-wide cohort analysis of factors affecting outcome of DCD kidney transplants demonstrated that prolonged CIT is associated with poorer outcome with doubling of the risk of graft failure for CIT beyond 12 hours. CIT was also the only variable that was potentially modifiable (Summers et al., 2010).

Another cohort study that explored the effect of donor age and CIT on outcome comparing kidneys from DCD and DBD donors in the UK showed that prolonged CIT was associated with reduced graft survival for DCD but not DBD kidneys. DCD kidneys showed more susceptibility to cold ischemic injury as longer CIT was associated poorer graft survival. DGF was significantly higher in kidneys from DCD donors (49%) than those from DBD donors (24%) (Summers et al., 2013).

A French cohort study of relationship of CIT with the transplantation outcomes in DBD kidney transplants highlighted the importance of CIT by demonstrating a strong and proportional increase in the risk of graft failure for each additional hour of CIT. It also showed a proportional relationship between each additional hour of CIT and the risk of recipient death (Debout et al., 2015). This relationship that associates

even a small increase in CIT with worse outcome has been highlighted in a subsequent commentary (Ponticelli, 2015).

Other studies have highlighted different thresholds for CIT beyond which the risk for graft failure increased (Johnson et al., 2010b, Summers et al., 2013, Kayler et al., 2011a, Opelz and Dohler, 2007). Data from the outcome of a large multinational collaborative study of 91,674 deceased donor kidney transplants shows that CIT beyond 18 hours threshold is detrimental to the graft outcome. The study also supports and justifies the exclusive use of simple cold storage as a means for preservation (Opelz and Dohler, 2007). Similar study by Doshi et al on paired kidneys showed progressively worsening effect on early graft outcome with CIT beyond 12 hours (Doshi et al., 2011).

#### **1.14.2 Implications of prolonged Cold Ischaemia Time on kidney transplant outcomes**

There is a plethora of evidence in published national and international studies demonstrating the association between prolonged CIT and its effect on short and long-term graft function, graft survival and acute rejection in deceased donor kidney transplants. Several studies have shown that CIT is an independent risk factor for DGF (Ojo et al., 1997, Doshi et al., 2011, Tandon et al., 2000). Whilst the association between prolonged CIT and short-term outcome is well established its impact on long-term graft outcome is less clear.

A study reviewing the implications of prolonged CIT identified its negative effect on the short-term graft outcome, especially with ECD and DCD kidneys, but it had no effect on long-term function and graft survival. It also found that DGF was associated with higher rate of acute rejection (AR) (van der Vliet and Warle, 2013). A retrospective cohort study of 5382 kidney recipients using United Network for Organ Sharing (UNOS) data on paired kidneys showed that the one that developed DGF had longer CIT. This was confirmed by multivariate analysis. DGF was also associated with AR in the first 6 months in a third of the recipients (Doshi et al., 2011).

Another cohort study of paired kidneys transplanted on 14 230 different recipients using data from Scientific Registry of Transplant Recipients showed that the incidence of DGF was significantly associated with longer CIT in ECD kidneys. However, it did not have any effect on graft survival and there was no association of AR with CIT (Kayler et al., 2011a).

A single-centre retrospective study by Mikhalski et al of 611 kidney transplant recipients who received modern immunosuppressive therapy demonstrated that longer CIT was an independent predictor for DGF by multivariate analysis. Prolonged CIT but not DGF was also an independent predictor of AR in multivariate analysis with 4% increase in the risk of AR with each additional hour of CIT. It was also an independent predictor of graft loss with respect to death-censored graft survival caused by its impact on AR (Mikhalski et al., 2008).

Another single-centre study by Quiroga et al concluded that CIT was the most important independent predictor of poor short and long-term graft survival with significant influence on DGF and graft survival. There was no specific threshold for CIT beyond which its deleterious effect accelerated but its effect appeared to be linear with progressive increase in the incidence of DGF with each additional hour, even at short CIT (Quiroga et al., 2006).

Longer CIT was shown to be associated with increased risk of DGF and AR and had a long-term impact on graft function and survival in another single centre study (Bronzatto et al., 2009).

A retrospective study of a cohort of 6322 recipients of DBD and DCD kidneys using Dutch Organ Transplant Registry data also found that CIT was an independent risk factor for DGF in multivariate analysis with shorter CIT associated with better graft survival in both DBD and DCD recipients (van der Vliet et al., 2011).

Poorer long-term graft survival was seen in a Spanish retrospective cohort study of 1395 deceased donor kidney transplants evaluating the association between the duration of CIT and graft outcome in younger donors (<50 years). It found that there was a marked association between longer CIT and death-censored graft failure independent of AR and DGF. Recipients with longer CIT also had an increased rate of AR, DGF and graft loss. They also found a linear association between increase in CIT and graft failure with 20% increase in graft failure for every 5 hours increase in CIT, most marked above 19 hours (Hernandez et al., 2008).

Ojo et al, in a multivariate analysis of data from the US Renal Data System, showed that prolonged CIT was the most important predictor of DGF with 23% increase in the risk with every 6 hours increase of CIT. DGF had a linear relationship with CIT, the risk of which increased with increasing CIT. DGF and AR were strong independent predictors of short and long-term graft failure. Prolonged CIT was also found to be an independent risk factor for reduced long-term graft survival (Ojo et al., 1997).

A systematic review and meta-analysis to determine the association between DGF and graft outcomes found detrimental association of DGF on long-term graft function and survival and AR (Yarlagadda et al., 2009).

A large, prospective, multicentre study in France revealed that CIT of >12 hours was an independent and significant factor in reduced long-term graft survival in ECD transplants (Aubert et al., 2015).

Several other studies have also demonstrated direct or indirect association between CIT and short and long-term outcomes in deceased donor kidney transplants (Warle et al., 2009, Roodnat et al., 2003, Asderakis et al., 2001, Bronzatto et al., 2009, McLaren et al., 1999, Connolly et al., 1996).

Despite this evidence, and although it is long established that prolonged CIT predisposes to DGF, CIT as an independent predictor for long-term graft outcome is still debated (Aubert et al., 2015, Kayler et al., 2011a, Kayler et al., 2017, Wang et



al., 2017). A multivariate analysis using data of a cohort of 18 164 paired kidneys from Scientific Registry of Transplant Recipients showed no difference in graft survival regardless of the difference in the length of CIT of 15 hours or more between the two kidneys. This was demonstrated in spite of a strong association between longer CIT and DGF but not between CIT and AR (Kayler et al., 2011b).

Another retrospective cohort study of paired kidneys from DCD donors transplanted into two separate recipients with different CITs, with data from US registry, found no effect of prolonged CIT on long-term graft outcomes. Also, there was no association between CIT and AR in the study (Kayler et al., 2017). Similar outcome was also seen in a UK study of impact of CIT on transplant outcomes in DCD kidneys where prolonged CIT did not affect patient and graft survival or long-term graft outcome (Pine et al., 2010). Another UK study of sequential paired DCD kidney transplants showed similar results. Although kidneys that were transplanted later had a higher incidence of DGF, this did not affect long-term graft or recipient survival (Goldsmith et al., 2010).

It is evident from the majority of these studies that there is a clear need to ensure that CIT remains as short as possible because poorer graft outcome increases morbidity, prolongs hospital stay, necessitates further immunosuppression and dialysis with significant financial ramifications.

There are several other risk factors that can also impact on outcomes following deceased donor kidney transplants. These include donor factors such as donor body

weight, donor age, donor type, e.g., DBD, DCD, ECD, number of previous grafts; recipient factors such as recipient body weight, waiting time on dialysis prior to transplant and HLA mismatches (Jung et al., 2010, Barlow et al., 2009, Johnson et al., 2010b, Pieringer and Biesenbach, 2005, Goh et al., 2009, Summers et al., 2010).

In the current climate of improving immunosuppression and increasing use of DCD and ECD kidneys to narrow the gap between demand and supply, CIT remains one of the few modifiable risk factors that can reduce the negative impact on these kidneys when there is little choice (Perico et al., 2004, Bahde et al., 2014).

### **1.14.3 What are the factors that affect Cold Ischaemia Time?**

Although there are several studies exploring the impact of prolonged CIT, there are only a few that investigate factors that contribute to CIT.

A French study analysed the influence of using a timesheet on CIT over a 2-year period and compared the result with the preceding 2 years. The individual timesheet for each kidney transplant was adapted to record time of interventions by all department personnel involved. Several parameters were collected and analysed to identify points of delay. Interestingly, they managed to significantly reduce the median CIT simply by implementing the timesheet, from 21.45 hours in the previous 2 years to 13.27 hours. The major limiting factor for transplant was the availability of theatre for transplantation (Vacher-Coponat et al., 2007).

In another French study, Joseph et al studied various stages of kidney retrieval process to transplantation. The time at which tissue was obtained for typing, which was performed at the time of kidney retrieval, was the principal factor that prolonged CIT. This could be reduced by 7 hours if HLA typing and crossmatching was performed while the donor was still in intensive care unit rather than during organ retrieval (Joseph et al., 2003).

A Chilean study investigating modifiable factors at various stages of kidney transplant identified a number of organisational and logistical issues and crossmatching policy that affect transplant outcomes. They found that by obtaining samples for HLA typing and crossmatching before retrieval was important in shortening the CIT. The shortest CITs were observed in kidneys transplanted locally when samples were sent locally for HLA typing and crossmatching (Elgueta et al., 2010).

Salahudeen et al demonstrated reduction of CIT during a 10-year study period in the US associated with improved kidney transplant outcomes despite lack of policy on procedural changes having been instituted to minimise CIT. They speculate that exogenous factors such as improved communication, better laboratory facilities, speedier transportation, greater efficacy in retrieving, transporting and transplanting could be attributed to decreased CIT. There was a possibility that transplant communities were perhaps aware of the ongoing study and were mindful of avoiding prolonged CIT in the context of increasing use of DCD and ECD kidneys (Salahudeen and May, 2008).

A retrospective Korean study of deceased donor kidney transplants showed a remarkably short mean CIT of  $3.8 \pm 2.2$  hours, which is markedly shorter than CITs in studies from other countries. This was attributed to several factors, namely, starting retrieval surgery only after completion of kidney allocation, short travelling distance within the specified national regions, simultaneous preparation of recipient at the time of donor surgery and prompt transplantation after kidney delivery and back-table preparation (Kim et al., 2013).

Ziaja et al also showed that early donor lymph node retrieval and local or central HLA typing and crossmatching significantly shortened CITs. (Ziaja et al., 2006)

A Hungarian study demonstrated that with protocol changes for donor HLA typing and prospective crossmatching using donor peripheral blood before declaration of brain death and, with recipient preparation starting before retrieval surgery, it was possible to significantly reduce CIT (Inotai et al., 2012).

## 1.15 Summary

Kidney transplant is a highly effective treatment for many patients with end stage renal failure. The shortage of organs for donation remains a major challenge, and has led us to accept organs for transplantation that we would have declined a decade ago. With increasing use of organs from DCD and ECD donors, it is beholden upon us to optimise the outcomes from each transplant. Cold ischaemia time is one of the few modifiable factors affecting outcome of kidney transplant.

This study sought to investigate factors that affect CIT in the process of deceased donor kidney donation and transplantation to identify areas for improvement.

Aims:

The aims of the present study were:

- To undertake comprehensive review of logistical factors in transplant centres in the UK and, their impact on CIT in deceased donor kidney transplants
- To determine whether there are specific areas to focus efforts on to reduce CIT
- To put forward proposals about how to reduce CIT across the UK

## **2 Methodology**

### **2.1 Study design**

This is a prospective, longitudinal study of logistical factors influencing cold ischaemia times in deceased donor kidney transplants performed over a 14-month period between 1<sup>st</sup> June 2011 and 31<sup>st</sup> July 2012. This included kidney only (single, double, en-bloc) and simultaneous pancreas and kidney (SPK) transplants from donation after brain death (DBD) and donation after circulatory death (DCD) donors and excluded living donor kidney transplants, kidneys transplanted with organs other than pancreas and transplants that did not proceed despite retrieval of organs. When 2 kidneys were transplanted in a single recipient (dual kidney transplant), the one with the longer cold ischaemia time (CIT) was excluded. Data on recipients and theatre times that were inconsistent with the rest of the data and those that had a discrepancy of more than 1 hour from NHSBT data were excluded (n=52 transplants).

The study was funded from a research grant from National Health Service Blood and Transplant (NHSBT), and was approved by the Kidney Advisory Group, which advises NHSBT on aspects of kidney transplantation within the United Kingdom.

## **2.2 Project collaboration**

A steering group was formed, exclusively for the study, which included Consultant Transplant Surgeon and Consultant Clinical Scientist from University of Edinburgh, Professor of Transplantation Surgery and Consultant Clinical Scientist from University of Cambridge, Principal Statistician from NHSBT and Clinical Fellow. The group met at key periods of the study at the interval of 3 to 6 months. It met initially to inform the overview of the study and to discuss practicalities and development of proforma for data collection, then to finalise the proforma and to plan the next steps to take the project forward. The group met again on completion of the study to analyse the results and to inform the findings. There were also regular weekly meetings between the Clinical Fellow and the supervisors to provide an update on the progress of the study, to discuss and address difficulties encountered in the process and to plan the next steps to move the study forward.

## **2.3 Measurements**

The variables included in the data were continuous and categorical data. Continuous data included series of time intervals between donor notification and completion of transplantation surgery. Categorical data included type of donor, transplant units, Histocompatibility and Immunogenetics (H&I) laboratories, type of crossmatch, transport of organs, mode of recipient travel, and hospital where transplants were performed.

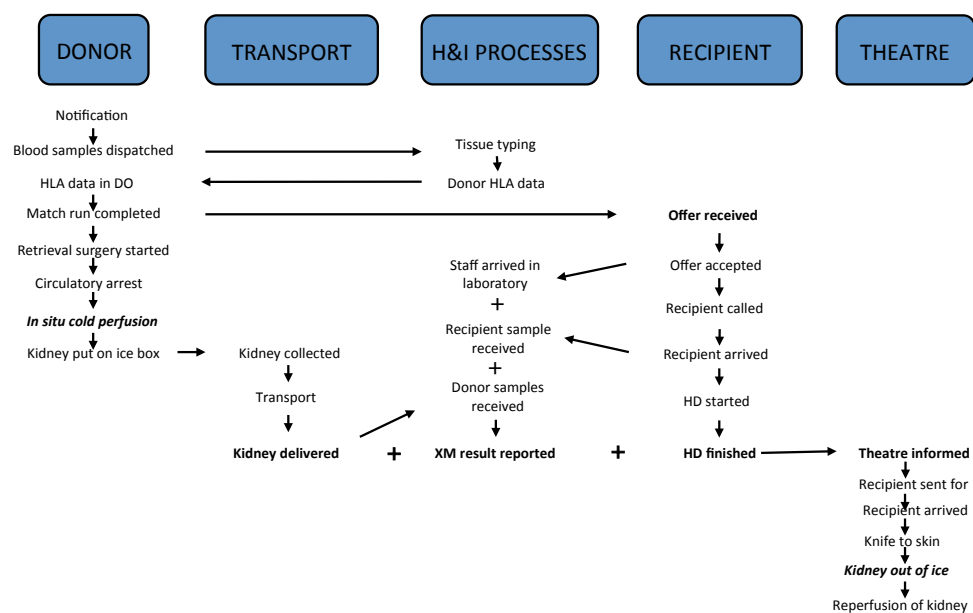
## **2.4 Kidney timeline**

Study of all aspects of kidney journey from donor to recipient formed the basis of the study. Questionnaires were developed to capture the crucial points on the kidney timeline for each deceased donor (DD) kidney from time of donation at donor hospital to completion of transplantation in recipient.

Five key logistical areas were identified, namely, activities around donor operation (Donor), organ transport (Transport), laboratory tests (H&I), recipient preparation (Recipient) and theatre (Theatre). Different factors within each of these key areas were examined to identify those that impacted on CIT. (Figure 2.1)



**Figure 2.1 Summary of logistical factors that might contribute to cold ischaemic time, divided into 5 key areas<sup>1</sup>**



<sup>1</sup> H&I processes may take place at different laboratories

## **2.5 Involvement of Organ Donation and Transplantation (ODT), NHS Blood and Transplant (NHSBT) and the Duty Office (DO) services**

At the outset, a visit to the Organ Donation and Transplantation (ODT) and NHSBT in Bristol was undertaken.

The aim of the visit was -

- To gain knowledge of how the Duty Office works
- To gain knowledge of support the statistical division provides for transplantation
- To gain knowledge of available data from the National Transplant database
- To find out how data could be accessed and how they should be analysed
- To identify key personnel for involvement in the study
- To identify information already collected by ODT to avoid duplication of data collection

At the time of the visit, anonymisation of donor and recipient details and methods to ensure accurate data collection was obtained for timings were discussed. It was agreed that some of the information could be added to the ODT form for donor information. Ways of obtaining information for transport times was discussed and agreed to contact the transport providers, including Transport for Transplant (TFT) and Amvale, to see what information they collect. An outline for data protection was

agreed following discussion with the Data Protection Information Manager at ODT and documented for each stage of the study.

## **2.6 Data protection**

Following discussion with the ODT Information Manager, the following measures were agreed upon and adopted to ensure data protection:

1. All donor and recipient details were fully anonymised by using only unique donor and recipient ODT numbers so that the data set would not contain any patient identifiable information.
2. The main database was stored in NHS Lothian computer with central server backup on a shared drive with controlled access. It was only accessible to the student and the supervisors. Data were also stored in the encrypted University laptop provided.
3. All the paper records were kept in the cabinet of a locked room at the Royal Infirmary of Edinburgh throughout the study period.
4. On completion of the study, the paper and electronic records would be returned to NHSBT for disposal.

## **2.7 Ethical approval**

Advice was sought for ethical approval from the South East Scotland Research and Ethics Service. It was informed that the study did not require NHS ethical approval under the terms of the Governance Arrangements for research Ethics Committees in the UK. (Appendix 2)

## **2.8 Pilot study**

A pilot study was set up to find out whether the data collection forms were fit for purpose and to identify areas of difficulties that would have to be addressed to ensure accurate and timely collection of relevant data. It was undertaken for 4 months between January and end of April 2011. The study was introduced locally to the transplant team including transplant surgeons, nephrologists, SN-ODs and recipient coordinators. Four transplant centres, (Edinburgh, Cambridge, Glasgow and Nottingham) and their associated H&I laboratories (Edinburgh, Cambridge, Glasgow and Sheffield) and Oxford H&I laboratory piloted the study. Two Regional Donor Coordinator team (Scottish Organ Donation and Eastern Regional Organ Donation) serving the participating centres also participated. Each of the piloting centres was visited personally to introduce the study and to encourage participation. The overview of the study was introduced and the data collection forms were explained to the lead for each centre and as many of the team members as possible. A key contact person was identified in each centre and communicated with regularly to address any queries or difficulties.

A link person was identified in each centre to take the ownership of the process. A dry run of data collection was undertaken with one of the local Recipient Coordinators before piloting in other centres.

At the time of collecting data, the teams were regularly given feedback with information about the gaps in the information provided in the data forms and they were encouraged to complete them as much as possible.

### **2.8.1 Participating centres in the pilot study**

Transplant centres –

1. Edinburgh
2. Cambridge
3. Glasgow
4. Nottingham

H&I laboratories –

1. Edinburgh
2. Cambridge
3. Glasgow
4. Oxford
5. Sheffield

Regional organ donation services

- 1** Scottish region
- 2** Eastern region

### **2.8.2 Findings of the pilot study and subsequent amendments**

The number of completed forms was compared with the NHSBT data on the total number of transplants that were undertaken within that period for each centre. The level of participation of each centre was thus assessed. Each form was also scrutinised for completeness of the data provided.

Feedback relating to the data forms was examined and pared down to simplify them to ensure maximum participation and completion.

## **2.9 Questionnaires**

Initially, 4 separate sets of questionnaires, one for each team of SN-ODs, H&I staff, transport personnel and recipient coordinators/transplanting surgeons were designed to encapsulate critical events along the kidney timeline. We studied the data available from ODT. The data already collected by ODT were removed from the proforma to avoid unnecessary duplication of effort. Effort was made to ensure that the proformas were simple and comprehensive.

As most of the information around the process of organ donation at donor hospital was already available from ODT data collection form it was decided that two more data points required for the study should be added to the form thus removing the necessity for a separate SN-OD form. It was also agreed that additional data relevant

to the study on transplants and transport would be provided on a monthly basis by ODT.

Finally, data collection for each DD kidney donation and transplant were narrowed down to 3 separate sources, which were then amalgamated to provide a complete picture encompassing the whole kidney journey.

The 3 principal sources for data collection were –

- ODT – provided data on monthly national transplant activities, donor activities and 3 monthly data on transport for transplant (TFT).
- H&I forms – provided data on activities around crossmatch
- Recipient forms – provided data on activities around recipient preparation and transplantation.

The data collection forms were ratified by the steering group, with final approval from the supervisors. The questionnaires were then rolled out and distributed to all participating centres. These were returned to the principal investigator after completion, via electronic mail, fax or post. (Appendices 3, 4, 5,6)

## **2.10 Dissemination of study information**

Newsletters were also distributed to all centres to provide an update on their hard work and insight into their own performance. Leaflets with information on the study were also distributed at the Annual British Transplantation Society Conference to raise awareness of the study. (Appendices 8, 9)

## **2.11 Multicentre engagement**

### **2.11.1 Centre visits**

Over a one-year period, 21 transplant units, 19 H&I units and 2 Donor Transplant Coordinator teams in the UK were individually visited in preparation for participation in the study. The aim of the visits was to introduce the study and to encourage full participation.

The head of each unit was first contacted via email to inform them about the study and to request to arrange a meeting with as many of their staff members as possible. To ensure the presence of maximum number of staff and for minimum disruption to their work, slots were requested to fit into one of their own monthly meetings where possible. Also, efforts were made to arrange visits to both the transplant units and their supporting regional H&I units on the same day. An overview of the study was presented to each team and was discussed with individuals who would require to complete the forms at each stage of the kidney journey, including SN-ODs, recipient



coordinators (RCs), transplant surgeons, specialty registrars (SpRs), clinical fellows, nephrologists, clinical scientists and staff at tissue typing laboratories.

### **2.11.2 Kidney transplant centres**

21 out of the 22 kidney transplants units in the UK were visited. One agreed to participate in the study without a visit. Belfast City Hospital was not included. 16 out of the 22 invited transplant centres signed up to the study.

- Birmingham Queen Elizabeth Hospital
- Bristol Southmead Hospital
- Cambridge Addenbrooke's Hospital
- Coventry University Hospital
- Edinburgh Royal Infirmary
- Glasgow Western Infirmary
- Leicester General Hospital
- London – Guy's Hospital and Great Ormond Street Hospital
- London – St George's Hospital
- London – Royal Free Hospital
- London – West London Renal and Transplant Centre
- Nottingham City Hospital
- Oxford Churchill Hospital
- Plymouth Derriford Hospital
- Portsmouth Queen Alexandra Hospital
- Sheffield Northern General Hospital

### **2.11.3 Histocompatibility and Immunogenetics units**

19 H&I units supporting all 22 transplant centres were visited and all signed up to the study.

- Birmingham NHSBT
- Bristol Southmead Hospital
- Cambridge Addenbrooke's Hospital
- Edinburgh SNBTS
- Glasgow Gartnavel Hospital
- Leeds St James's University Hospital
- Leicester General Hospital
- Liverpool Royal Liverpool University Hospital
- London – Guy's Hospital
- London – Royal Free Hospital
- London – Hammersmith Hospital
- London – Tooting
- Manchester Royal Infirmary
- Newcastle NHSBT
- Northern Ireland Blood Transfusion Service
- Oxford Churchill Hospital
- Plymouth Derriford Hospital
- Sheffield NHSBT
- Wales Welsh Blood Service

#### **2.11.4 Regional donor transplant coordinator teams**

It was agreed that relevant donor data would be included in the NHSBT form already used by all 12 regional donor transplant coordinator teams.

- Eastern Region Cambridge
- London Region London
- Midlands Region Birmingham
- Northern Ireland Region Belfast
- North West Region Liverpool
- Northern Region Newcastle
- Scotland Region Falkirk
- South Central Region Oxford
- South East Region West Sussex
- South Wales Region Cardiff
- South West Region Exeter
- Yorkshire Region Leeds

## **2.12 Deceased donor kidney transplant logistics**

Visits to transplant centres across the country provided a unique insight into variation in local practices and procedures and revealed complex and multifactorial nature of the logistics of DD kidney transplant in the UK.

There were variations relating to structure and modus operandi of a number of transplant centres, H&I units and transport providers.

### **2.12.1 Transplant centres**

In Liverpool transplant unit, SpRs take the calls instead of the RCs whereas in Leicester, the Professor takes the calls and SpRs prepare recipients. RCs are only available during normal working hours in Liverpool and Leeds. In Glasgow, consultant transplant surgeons take the calls and SpRs out of hours. There are no RCs at Royal London, Guy's or Royal Free transplant units. Transplant surgeons coordinate transplants at the Royal London. At the Royal Free nephrologists, transplant surgeons or clinical fellows take calls. Urologists may also be involved out of hours and, kidneys are delivered in theatre rather than on the ward. In Birmingham, RCs coordinate transplants but are not involved in theatre. In Plymouth and Sheffield, RCs work from home full time and in Newcastle, RCs take call out of hours from home. Coventry transplant unit is unique in that all DD transplants are performed the day after offer is received.

## **2.12.2 Histocompatibility and Immunogenetics units and virtual crossmatch policy**

Each H&I unit usually supports its regional transplant unit. Exceptions to this are Guy's H&I laboratory which supports 3 regional transplant units, namely, Guy's, St George's and Great Ormond Street Hospital (GOSH); St George's H&I laboratory (Tooting) supports St George's and Portsmouth transplant units; Sheffield H&I laboratory supports Sheffield and Nottingham transplant units; and Birmingham H&I laboratory supports Birmingham and Coventry transplant units.

Two out of the 19 H&I units did not practise vXM policy which were the regional H&I laboratories for Hammersmith and for Newcastle transplant units. In Liverpool, list of recipients suitable for vXM was available to transplant surgeons who make the decisions for suitable transplants with a vXM without the need for confirmation with the Consultant Clinical Scientist. H&I laboratories always performed retrospective crossmatch for all transplants with a vXM the next working day.

### **2.12.3 Transport**

The majority of transport facilities for transport of donated organs for transplant and blood and tissues for typing and crossmatching were provided centrally by Transport for Transplant (TFT) based in Birmingham. Liverpool, however, had their own local transport facilities for organs, bloods and tissues and were not involved with TFT.

### **2.13 Variation in local transplant centre practices**

An additional study to assess robustness of the support system in centres undertaking deceased donor (DD) kidney transplant was done while visiting all transplant centres. Information was collected with a view to identifying areas for improvement at local level that may help to achieve better transplant outcomes.

A supplementary questionnaire was designed to gain insight into any local variations in the current practices in UK transplant centres involved in DD kidney transplantation. During transplant centre visits, the lead or senior transplant surgeon in each transplant unit completed the questionnaire.

This observational study included data collected from 22 transplant centres.

Information on other organs transplanted in the unit, access to theatre including options for simultaneous DD transplant for 2 kidneys if required and whether they would cancel an elective kidney transplant for a DD kidney transplant, number of consultant transplant surgeons actively involved in DD kidney transplant, local

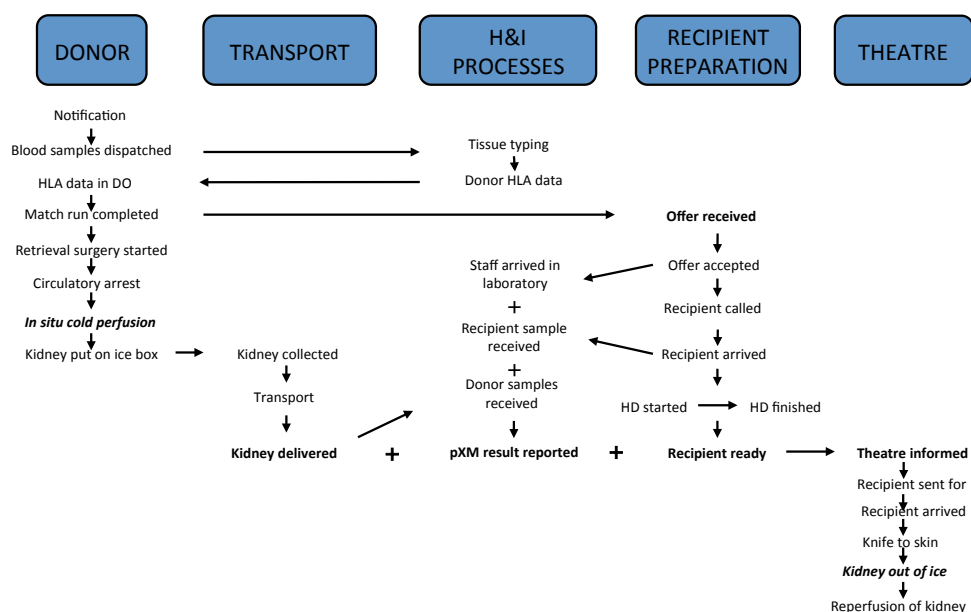
allocation policy, availability of a dedicated anaesthetic team, availability of theatre staff, number of dedicated ICU, HDU and ward beds available for DD kidney transplants, and other factors affecting ability to take the patient to theatre for transplant were recorded. (Appendix 7)

The data on variation in local practices included factors relating to the following –

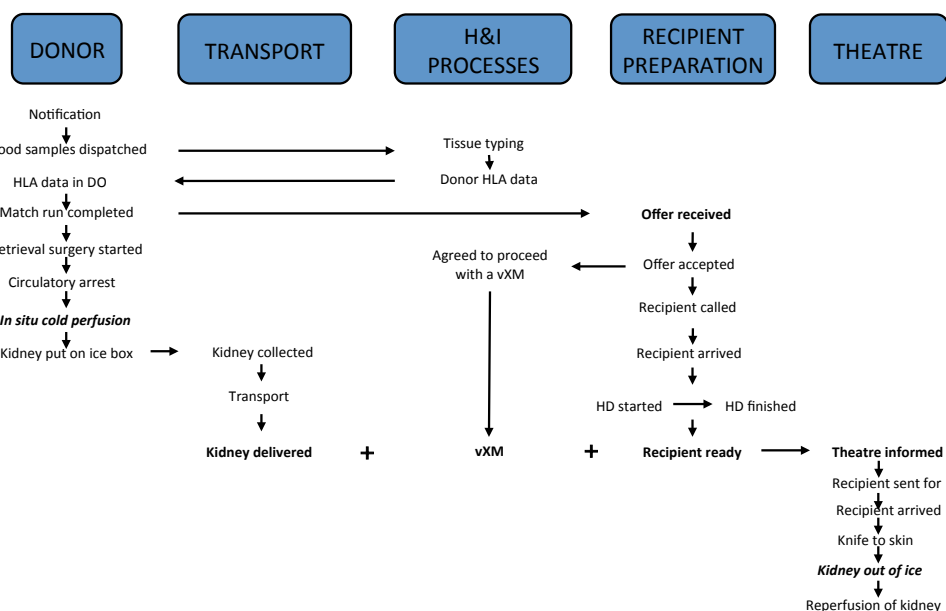
1. Multi-organ or Kidney only transplant centre
2. Manpower availability
3. Consultant transplant surgeons
4. Dedicated anaesthetic team
5. Theatre staff
6. Theatre availability
7. Theatre accessibility
8. Theatre practice
9. Local allocation policy for DCD kidneys
10. Access to H&I services
11. Recipient factors
12. Dedicated ITU/HDU/Ward beds

Two principal scenarios for kidney timeline were identified. (Figures 2.2 and 2.3)

**Figure 2.2 Transplants with pXM**



**Figure 2.3 Transplants with vXM**





## **2.14 Crossmatching Description**

Several centres in the United Kingdom have adopted selective omission of the pre-transplant crossmatching in potential recipients who are at low immunological risk, and this has been shown to be safe and effective at reducing CIT.

For clarification in this study the term pre-transplant crossmatching (pXM) is used for those transplants that required full crossmatch (XM) testing to be performed before start of surgery, and virtual crossmatch (vXM) for those in whom the prospective pre-transplant donor XM was omitted and it was safe to proceed without waiting for the XM test to be performed. The formal XM test was performed retrospectively, and there have been no cases of unexpected XM positivity after transplantation.

## **2.15 Data Collection**

Data were obtained on DD kidney only and simultaneous pancreas and kidney (SPK) transplants from the 16 transplant centres along with the 19 H&I laboratories, with the aim of determining whether there are specific areas on which to focus efforts to reduce CITs. All data were collected prospectively. At the end of each month of the study period, this was checked against the ODT data on transplantation for each centre. Every form was chased with emails sent out to each centre with a list of any outstanding forms to ensure full engagement as well as to encourage them to complete and return as many forms as possible.

The CIT was calculated from United Kingdom Transplant Registry data held by NHSBT. It was defined as the time from in situ cold perfusion in donor at the time of retrieval to the time of removal of kidney from ice for transplantation in recipient. This was available for all transplants performed in all 22 centres.

Factors that were considered to be relevant for this study were agreed with a national multidisciplinary team, including transplant surgeons, H&I scientists, and statisticians. In addition, draft documents were circulated to the heads of transplant centres for their input.

Categorical and continuous data were collected along the kidney timeline from the time of organ donation at the donor hospital to completion of transplantation at recipient hospital on 4 different data collection forms, focusing on five key logistical

areas, namely, donor operation, organ transport, laboratory tests, recipient preparation and theatre. Different factors within each of these key areas were examined to identify those that impacted on CIT.

## **2.16 Data Input**

A national database was set up and up to date data input was done prospectively. Data were checked for errors with frequency analyses and diagrams. Each outlier was examined by re-checking them against the original forms as well as with the rest of the data for the corresponding transplant. We excluded transplants that did not proceed despite retrieval of organs and the kidneys that were transplanted with organs other than pancreas. When two kidneys were transplanted in a single recipient (dual kidney transplant) the one with the longer CIT was excluded. Data on recipient and theatre times that were inconsistent with the rest of the data and those that had a discrepancy of more than 1 hour from NHSBT data were excluded (n=52 transplants). Transplants with no virtual cross-match (vXM) or prospective pre-transplant XM (pXM) information were excluded.

## **2.17 Data Cleansing and Quality Assurance**

Data cleansing was undertaken before the final analysis: 5% of the data were selected randomly at regular intervals, and each one was checked against the original forms and records to establish excellent quality assurance of the input data. An error rate less than 1% was considered acceptable. All time intervals were recalculated and corrected following data cleansing to maintain accuracy.

Information was available for all donors and crossmatch types, 37% of transports, 32% of recipients, and 35% of theatre activities, with varying levels of completeness of data for each activity..

## **2.18 Statistical Analysis**

All data for DD kidney and SPK transplantation were calculated for general demographics including number and type of donor, type of allocation, reallocation, crossmatching, transport of kidneys, recipient, theatre and kidney transplants were calculated. Various categorical factors and time intervals contributing to the total CIT were determined using univariate analysis using general linear model. The time intervals in the univariate analysis were calculated in hours. Several time intervals between process of donation and completion of transplantation were examined. These were times around the donation activities, retrieval surgery, organ transport, tissue typing and crossmatching, recipient preparation and theatre. Various categorical data were included in the analysis for donor, namely, donor type and

donor tissues used for pre-transplant crossmatching (pXM). Categorical data included for transport were mode of kidney transport and those included for H&I activities were type of crossmatch, types of donor tissues and recipient serum samples used for pXM. The categorical data for recipient included mode of recipient travel, requirement for haemodialysis immediately pre- transplant and requirement for current recipient serum sample for pXM. The categorical data included for theatre activities was type of theatre where transplant was performed. For each categorical and continuous variable, parametric tests with log transformation of CIT as the dependent variable were performed to assess their contribution to CIT. ANOVA test was used to perform univariate comparisons of transplants from DBD versus DCD donors and for transplants performed with a virtual crossmatch (vXM) versus pXM for all the categorical and continuous data. P-values of  $<0.05$  were considered significant. All univariate analyses were done with SPSS version 21.

Those categorical and continuous factors in pXM and vXM groups that were found to be significant in the univariate analyses were included in the multivariate model. The multivariate analysis included 97% of the data included in the univariate analyses as only transplants with complete data for CIT and type of crossmatch performed were included. The multivariate analyses were carried out by NHSBT statisticians using SAS.

## **2.19 Intercept Description**

The intercept is the median CIT if all other factors are set to zero (the baseline).

## **3 Results**

### **3.1 Introduction**

A total of 1763 transplants from 1037 donors performed within the 14-month study period were included. Of those, 41% were DCD and 59% DBD transplants. While the majority of the transplants were kidney-only transplants (90%), 10% were simultaneous pancreas and kidney (SPK) transplants. Kidney-only transplants included 59 pairs of double and en-bloc kidneys; the rest were single kidney transplants. Two recipients were transplanted twice within the study period.

The majority of kidneys (64.5%) were shipped from a different region (imports) and 35.5% were allocated either locally or regionally. Whereas DBD kidneys made up for the majority of imports (78.4%), most of the DCD kidneys were transplanted locally or regionally (76.8%). A small number of kidneys (2.4%) were reallocated, mostly, locally. (Table 3.1)

**Table 3.1 General demographics**

Demographics			n	(%)
Transplants	DBD		1036	(59)
	DCD		727	(41)
	Total		1763	
Kidney-only / SPK transplants	Kidney-only	Single kidney transplant	1527	(90)
		Double kidney transplant (including 4 En-bloc)	59 pairs	
	SPK		177	(10)
Dual/En-bloc kidney transplants	DBD		7 pairs	(11.9)
	DCD		52 pairs	(88.1)
Donors	DBD		619	(59.7)
	DCD		418	(40.3)
	Total		1037	
Recipients	1 transplant within study period		1759	
	2 transplants within study period		2	
	Total		1761	
Kidney Allocation	Local / Regional	DBD	145	(23.2) of local
		DCD	481	(76.8) of local
		Total	626	(35.5)
	Imported	DBD	891	(78.4) of import
		DCD	246	(21.6) of import
		Total	1137	(64.5)
Reallocated	No		1720	(97.6)
	Yes	Total	43	(2.4)
		Local	Once	(67.4) of reallocation
			Twice	(7.0) of reallocation
		Reallocated from other centre		11 (25.6) of reallocation

### **3.2 Review of current practices in UK transplant centres**

There was an average of 4 Consultant Transplant Surgeons in each kidney-only transplant centre and 6 in multi-organ transplant centres. 14 of the 22 centres had no dedicated anaesthetic team for deceased donor (DD) kidney transplants. Five centres had a dedicated anaesthetic team for day-time activity and one centre for out of hours transplants only. There was a dedicated anaesthetic team for DD kidney transplants both in and out of hours in only 2 centres; both of these centres are multi-organ transplant centres.

Six transplant centres would cancel an elective transplant in favour of a DD kidney transplant. Nine transplant centres had no facilities for simultaneous transplantation of two DD kidneys if it was required. Only 2 out of the 22 transplant centres have round the clock access to a dedicated transplant theatre while 15 centres have access to emergency theatre only for DD kidney transplants. (Table 3.2)



**Table 3.2 Logistical variations in local transplant centre practices**

Transplant centre logistics		Transplant unit		Total
		Kidney only	Multi-organ	
Dedicated anaesthetic team available for kidney transplant?	No	8	6	14
	In-hours only	2	3	5
	Both in and out of hours	0	2	2
	Out of hours only	1	0	1
Would you cancel elective transplant for a DD kidney transplant?	No	7	8	15
	Yes	3	3	6
	Not known	1	0	1
Options for doing simultaneous kidney transplant for two DD kidneys if required	No	8	1	9
	In-hours only	1	8	9
	Both in and out of hours	1	1	2
	Rarely	1	1	2
Access to theatre for DD kidney transplant.	Dedicated transplant theatre but in-hours only	1	4	5
	Dedicated transplant theatre both in and out of hours	1	1	2
	Access to emergency theatres only	9	6	15

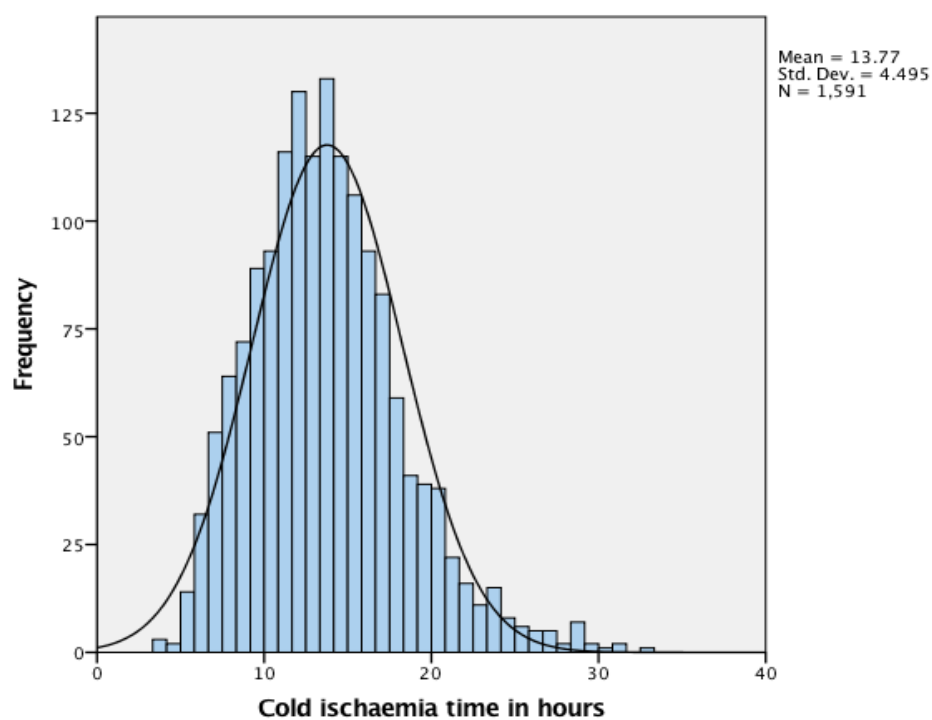
### 3.3 Cold ischaemia time

The number of transplants with known cold ischaemia time (CIT) was 1591 out of the 1763. The overall median CIT for kidney transplants in all transplant centres was 13.4 hours (SD 4.5, Interquartile range (IQR) 10.7-16.4). The shortest recorded CIT was 3.7 hours, and the longest was 33.1 hours. (Table 3.3, Figure 3.1)

**Table 3.3 Overall CIT**

Overall CIT in hours				
Mean	SD	Minimum	Maximum	Median (IQR)
13.8	4.5	3.7	33.1	13.4 (10.7-16.4)

**Figure 3.1 Overall cold ischaemia time**



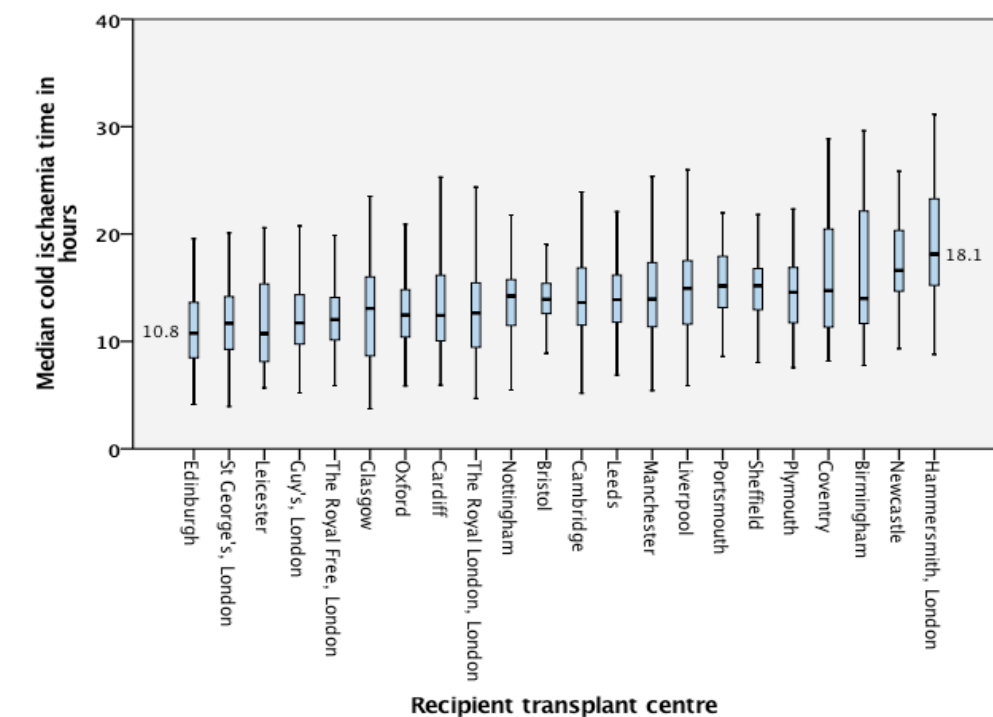
The difference in CIT between simultaneous pancreas and kidney (SPK) transplants and kidney alone transplants was not statistically significant (12.9 hours and 13.5 hours, respectively). ( $F=0.959$ ,  $p=0.328$ )

### 3.3.1 Cold ischaemic time by transplant centre

There was significant centre variation in mean CIT across the 22 UK transplant centres ranging from between 11.5 hours and 19.2 hours ( $F=10.193$ ,  $p<0.0005$ ).

Edinburgh had the shortest median CIT at 10.8 hours and Hammersmith the longest at 18.1 hours. (Table 3.4, Figure 3.2)

**Figure 3.2 Transplant centre variation in median cold ischaemia time**



**Table 3.4 Cold ischaemia time in UK transplant centres in hours (p<0.0001)**

<b>Recipient transplant centre</b>	<b>n</b>	<b>Mean</b>	<b>SD</b>	<b>Minimum</b>	<b>Maximum</b>	<b>Median (IQ Range)</b>
Cambridge	128	14.1	4.0	5.2	25.8	13.6 (11.5-16.7)
Oxford	147	13.0	3.7	5.9	28.2	12.5 (10.4-14.9)
Nottingham	85	13.8	4.1	5.5	24.2	14.2 (11.5-15.9)
Plymouth	26	15.1	4.6	7.6	29.4	14.6 (11.7-17.1)
Newcastle	43	17.5	4.3	9.3	31.3	16.6 (14.6-20.4)
Guy's	110	12.2	4.0	5.2	23.6	11.7 (9.7-14.3)
Hammersmith	40	19.2	5.3	8.8	31.2	18.1 (15.0-23.4)
Leicester	39	12.2	5.2	5.7	29.0	10.7 (8.1-16.5)
Manchester	159	14.4	4.4	5.4	28.9	13.9 (11.4-17.4)
Sheffield	39	15.1	4.8	5.6	33.1	15.2 (12.9-17.0)
Portsmouth	43	15.0	3.6	5.1	22.0	15.2 (13.1-18.0)
Birmingham	29	16.7	6.6	7.8	29.6	14.0 (11.4-22.8)
Edinburgh	77	11.5	4.0	4.1	24.4	10.8 (8.5-13.9)
Liverpool	80	14.8	4.7	5.9	29.1	14.9 (11.6-17.6)
Bristol	51	14.0	2.7	7.7	21.3	13.9 (12.6-15.4)
St George's	51	11.8	3.6	4.0	20.1	11.7 (9.1-14.3)
Leeds	96	14.4	4.1	6.9	30.3	13.9 (11.8-16.2)
The Royal Free	81	12.4	3.4	5.9	23.1	12.0 (10.1-14.1)
The Royal London	54	13.2	4.6	4.7	25.4	12.6 (9.4-15.7)
Coventry	13	16.0	6.2	8.2	28.9	14.7 (11.0-21.4)
Cardiff	99	13.1	4.2	5.9	25.3	12.4 (10.0-16.3)
Glasgow	101	12.7	4.5	3.7	23.5	13.1 (8.6-16.0)
Total	1591					

### 3.3.2 Cold ischaemic time in kidney-only and multi-organ transplant centres

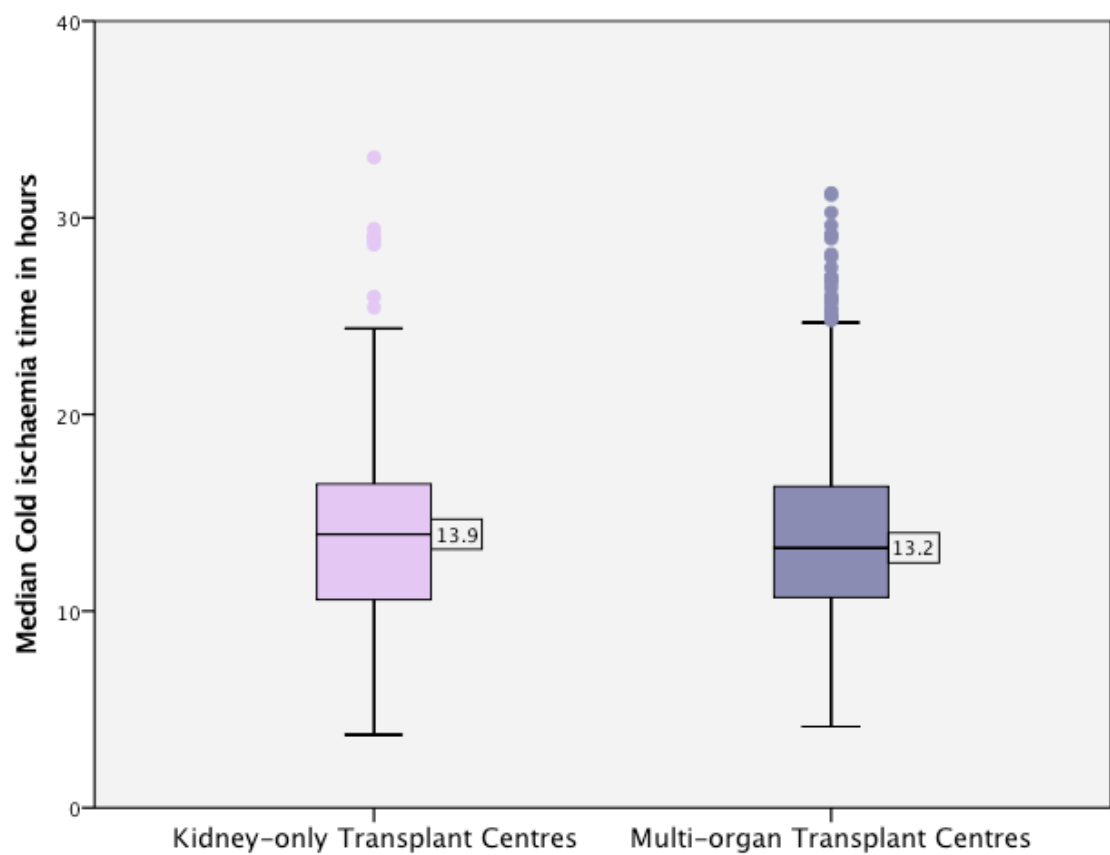
Half of the 22 UK transplants units perform deceased donor (DD) kidney-only transplants and the other half, the multi-organ transplant centres, also transplant other organs such as pancreas and / or liver and / or small bowel in addition to kidneys.

Comparison of CIT between kidney-only and multi-organ transplant centres did not show any significant difference (Mean 13.7 and 13.8, respectively,  $p=0.512$ ). (Table 3.5, Figure 3.3)

**Table 3.5 Cold ischaemia time in kidney only and multiorgan transplant centres**

Transplant Centres	n	CIT in hours				
		Mean	SD	Minimum	Maximum	Median (IQ Range)
Kidney-only	582	13.7	4.4	3.72	33.1	13.9 (10.6-16.5)
Multi-organ	1009	13.8	4.5	4.1	31.3	13.2 (10.7-16.3)

**Figure 3.3 Median cold ischaemia time in kidney only and multiorgan transplant centres**



### 3.3.3 Cold ischaemic time in relation to kidney allocation

#### (Local/Import)

Mean CIT for kidney transplants that were performed with kidneys imported from a different region (64.5%) was significantly higher than for those that were transplanted locally or regionally (35.5%) ( $p < 0.0005$ ). (Table 3.6, Figure 3.4)

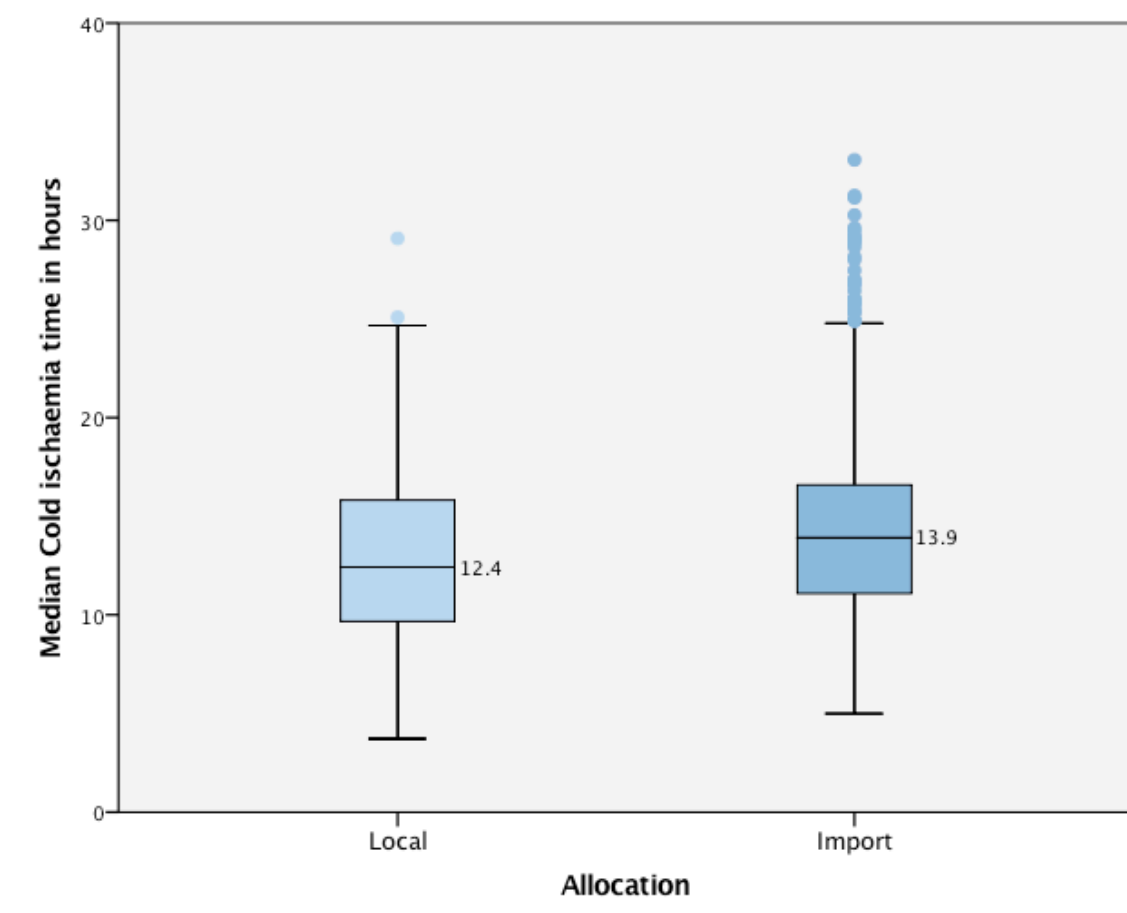
The majority of locally transplanted kidneys were DCD kidneys and 78% of imported kidneys were DBD kidneys.

**Table 3.6 Cold ischaemia time for local/regional and imported kidney transplants**

Allocation	n	CIT in hours				
		Mean	SD	Minimum	Maximum	Median (IQ Range)
Local	525	12.8	4.4	3.7	29.1	12.4 (9.6-15.9)
Import	1066	14.2	4.5	5.0	33.1	13.9 (11.1-16.6)

Significance:  $F=4.507$ ,  $p < 0.0005$

**Figure 3.4 Median cold ischaemia time for local/regional and imported kidney transplants**





### 3.3.4 Cold ischaemic time in relation to reallocation of kidneys

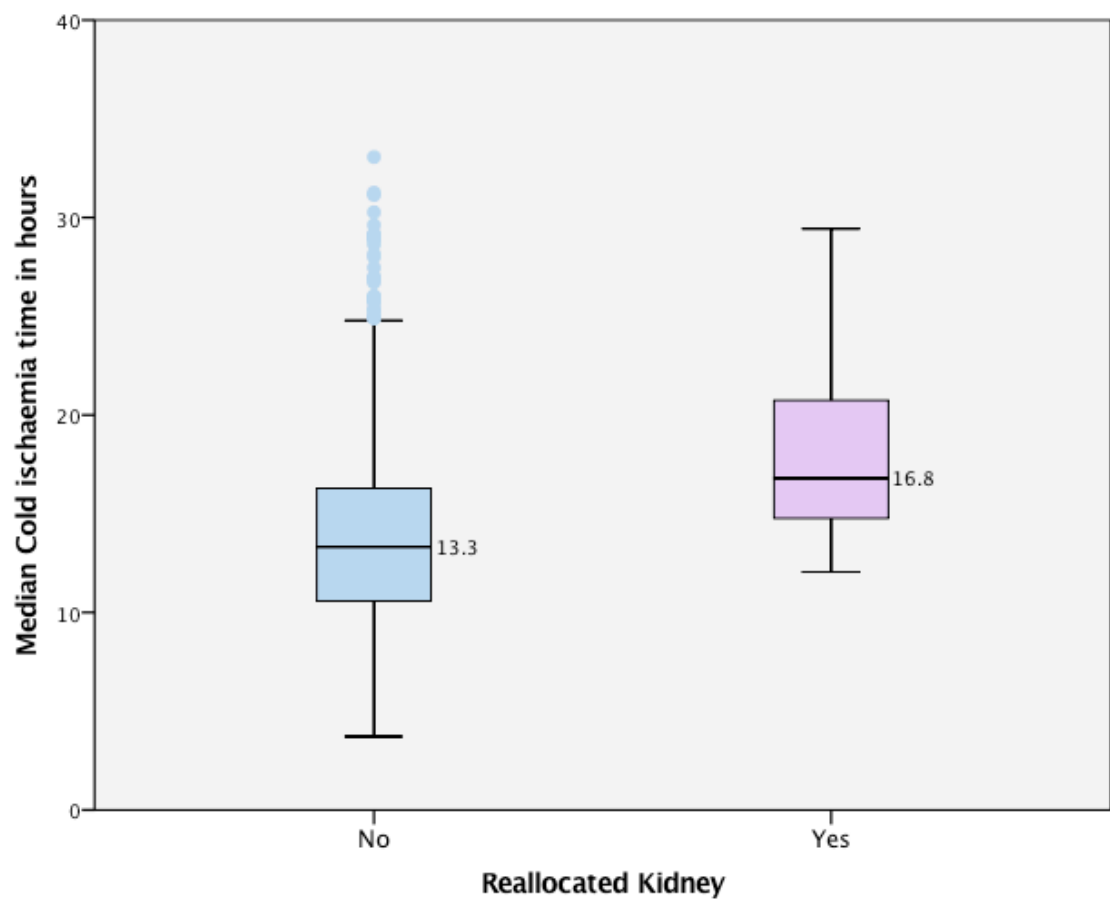
The number of reallocated kidneys was small (n=40). Reallocation of kidneys following their initial acceptance added 3.5 hours to median CIT ( $p<0.0005$ ). (Table 3.7, Figure 3.5).

**Table 3.7 Cold ischaemia time for reallocated kidney transplants**

Reallocated kidneys	n	CIT in hours				
		Mean	SD	Minimum	Maximum	Median (IQ Range)
No	1551	13.7	4.5	3.7	33.1	13.3 (10.6-16.3)
Yes	40	17.9	4.1	12.1	29.4	16.8 (14.7-20.9)

Significance:  $F=32.227$ ,  $p<0.0005$

**Figure 3.5 Median cold ischaemia time for reallocated kidney transplants**



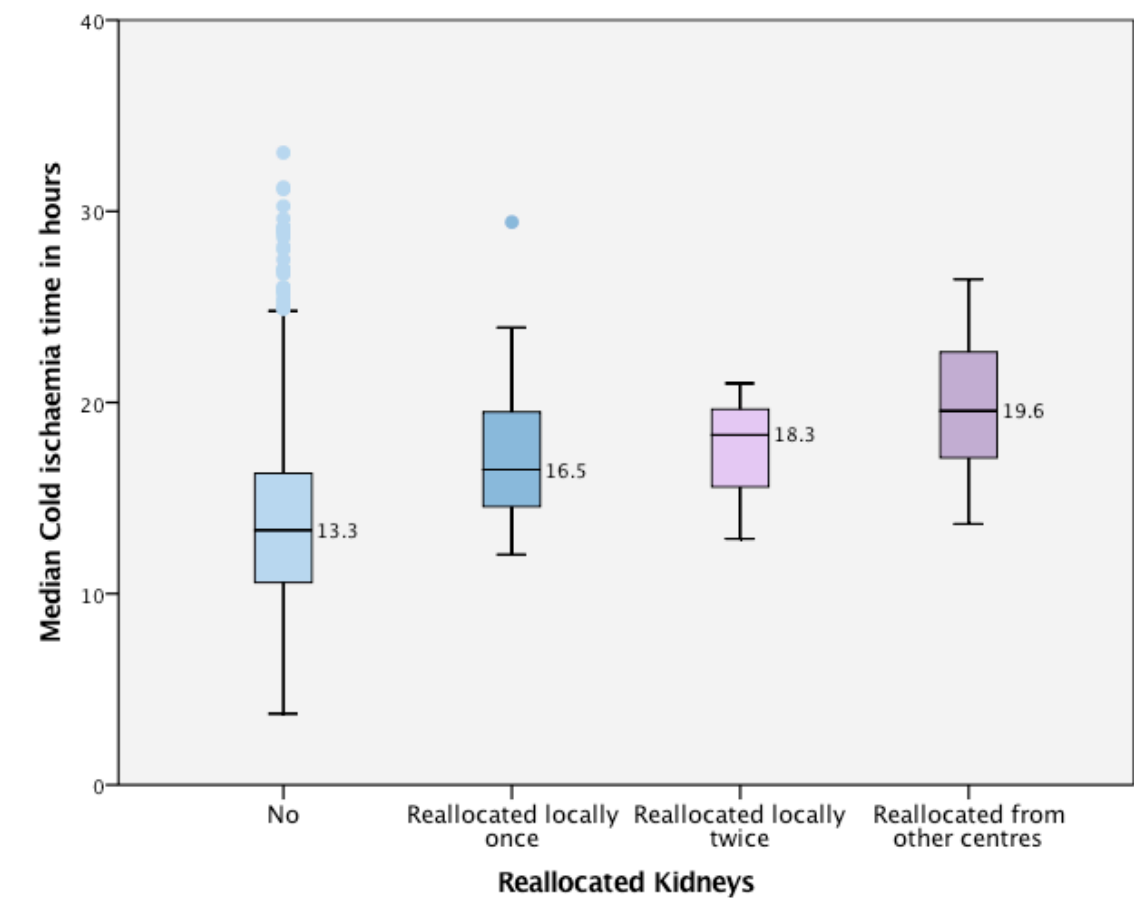
The median CIT for kidneys that were reallocated from a different transplant centre was significantly longer (6 hours) than for those that were reallocated a single time locally (3 hours) ( $p<0.0005$ ). (Table 3.8, Figure 3.6)

**Table 3.8 Cold ischaemia time in relation to type of kidney reallocation**

Reallocated Kidneys	n	CIT in hours				
		Mean	SD	Minimum	Maximum	Median (IQ Range)
No	1551	13.7	4.5	3.7	33.1	13.3 (10.6-16.3)
Locally once	26	17.1	3.9	12.0	29.4	16.5 (14.4-19.6)
Locally twice	3	17.4	4.1	12.9	21.0	18.3 (-)
From other centre	11	19.9	4.2	13.7	26.4	19.6 (16.6-22.9)

Significance:  $F=11.288$ ,  $p<0.0005$

**Figure 3.6 Cold ischaemia time in relation to type of kidney reallocation**



### 3.4 Donor factors and impact on cold ischaemia time

All donor data for activities around the donation process were available. There were 1037 deceased donors from whom 1763 kidneys were transplanted including 59 pairs of double and en-bloc kidneys, in a total of 1761 recipients (twice in 2 recipients). DBD and DCD donors constituted 59.7% and 40.3% of the total, respectively.

#### 3.4.1 Type of donor

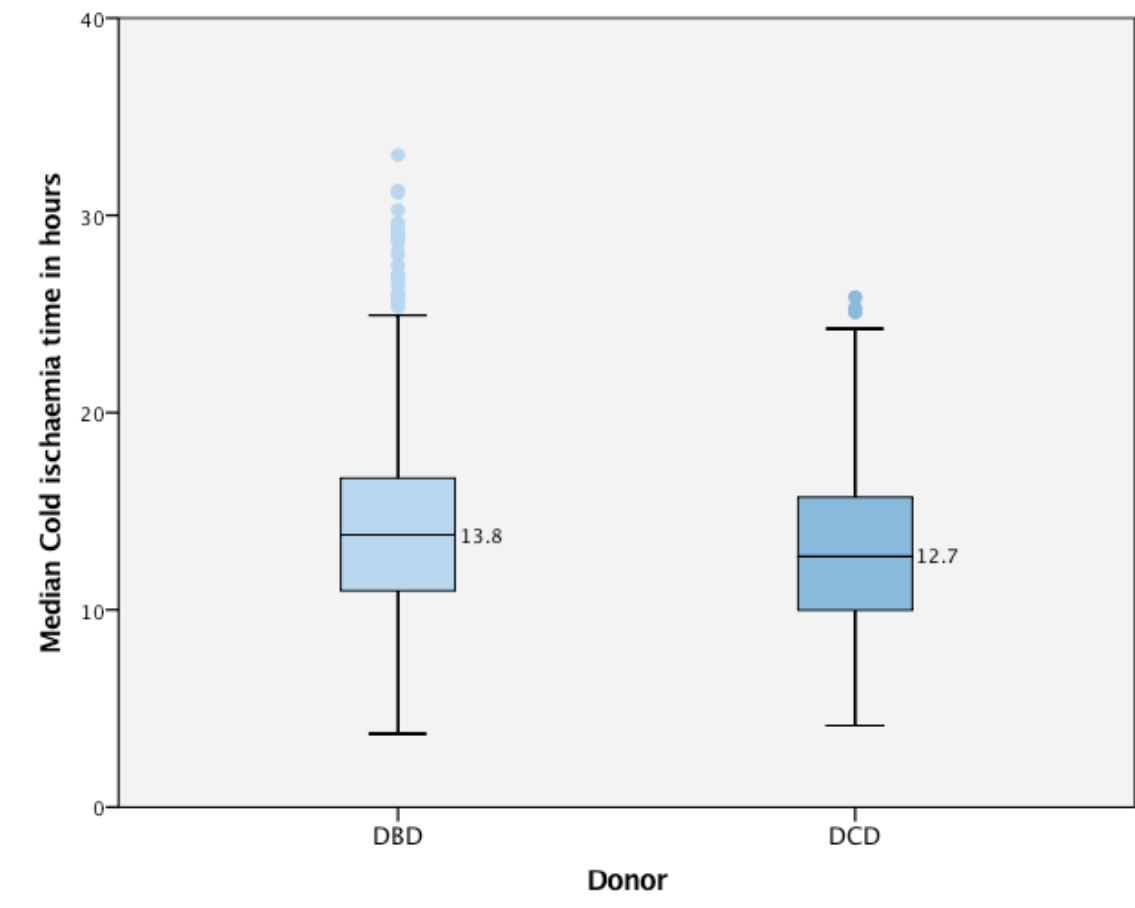
The median CIT for transplants with kidneys from DCD donors was significantly shorter than that for transplants with kidneys from DBD donors (12.7 hours and 13.8 hours, respectively) ( $p < 0.0005$ ) with some DBD kidneys being transplanted beyond 30 hours of CIT. (Table 3.9, Figure 3.7)

**Table 3.9 Cold ischaemia time for DBD and DCD donor kidney transplants**

Donor	n	CIT in hours				
		Mean	SD	Minimum	Maximum	Median (IQ Range)
DBD	987	14.2	4.6	3.7	33.1	13.8 (11.0-16.7)
DCD	604	13.0	4.2	4.1	25.9	12.7 (10.0-15.7)

Significance:  $F = 29.368$ ,  $p < 0.0005$

**Figure 3.7 Cold ischaemia time for DBD and DCD donor kidney transplants**



### **3.4.2 Centre variation in cold ischaemia time**

The number of transplants ranged between 13 in Coventry and 159 in Manchester. Whilst Leicester did not perform any DCD transplants, it ranged between 12% in Hammersmith and 78% in Plymouth. (Table 3.10)

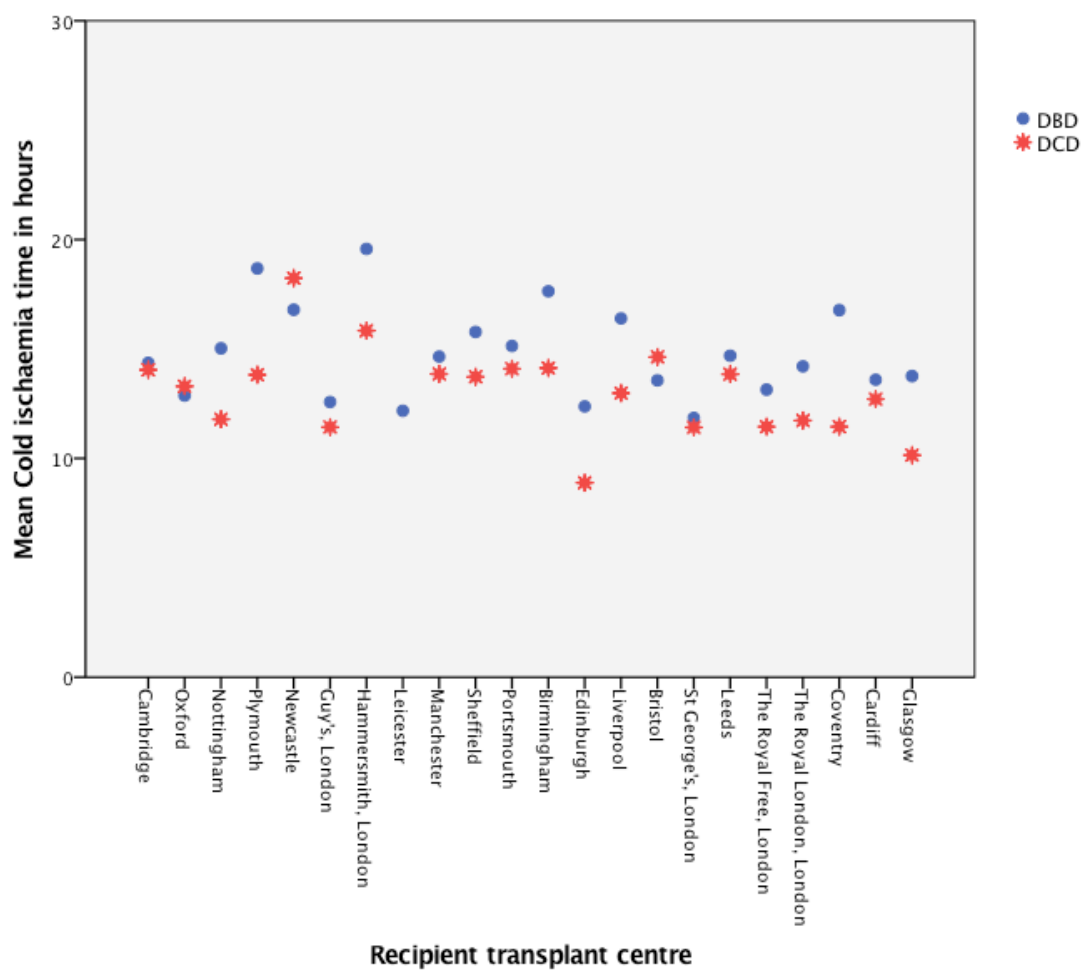
There was also significant variation in CIT between DBD and DCD kidney transplants within transplant centres ( $p < 0.0005$ ) with the largest difference seen in Glasgow where CIT was 6 hours shorter for DCD transplants. (Table 3.10, Figures 3.8 and 3.9)

Table 3.10 Transplant centre variation in cold ischaemia time for DBD and DCD donor kidney transplants (Significance:  $F=2.702$ ,  $p<0.0005$ )

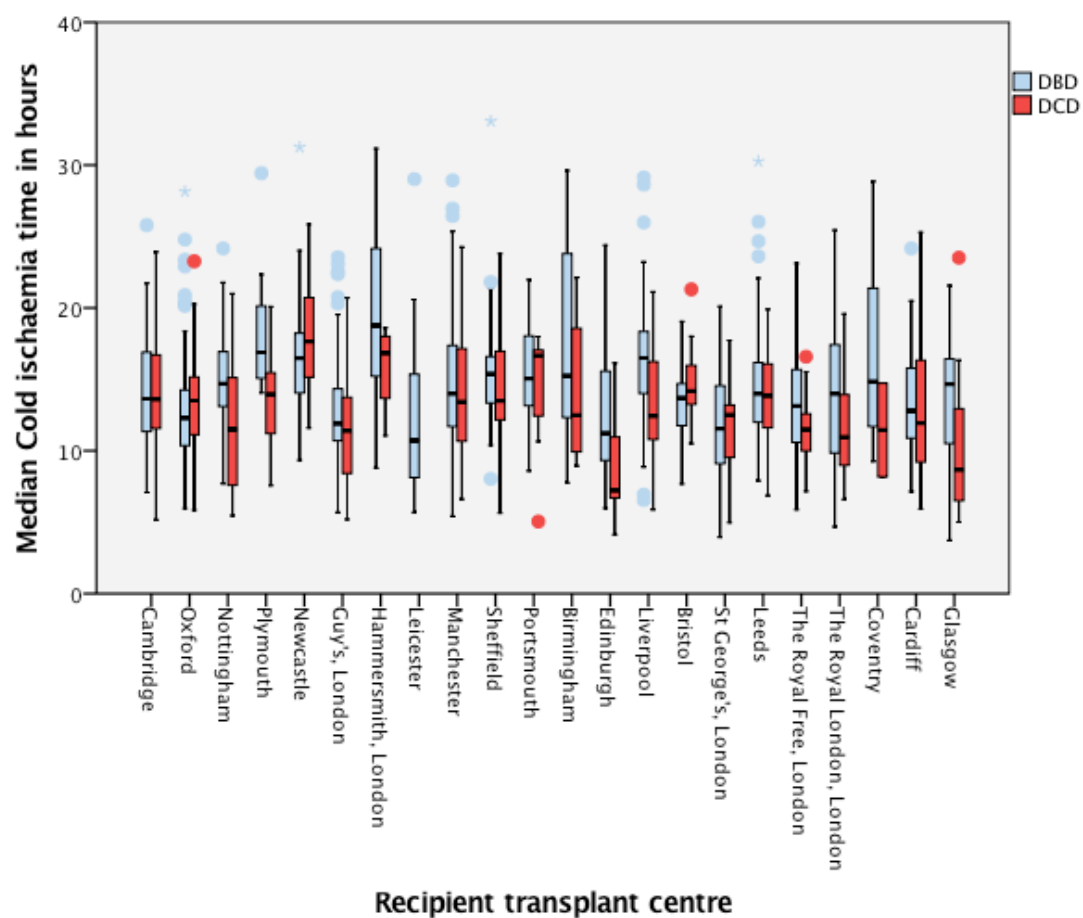
Recipient Transplant Centre	DBD				DCD			
	n	Mean	SD	Median (IQR)	n	Mean	SD	Median (IQR)
Cambridge	39	14.4	4.1	13.6 (11.4-16.9)	100	14.1	4.0	13.6 (11.5-16.8)
Oxford	104	12.9	3.8	12.3 (10.4-14.3)	52	13.3	3.6	13.5 (11.0-15.2)
Nottingham	52	15.0	3.3	14.7 (13.1-16.9)	36	11.8	4.4	11.5 (7.6-15.1)
Plymouth	8	18.7	5.5	16.9 (14.5-22.3)	29	13.8	3.5	14.0 (10.9-15.5)
Newcastle	21	16.8	4.8	16.5 (14.1-18.2)	45	18.2	3.9	17.7 (15.2-20.7)
Guy's	89	12.6	4.1	11.9 (10.7-14.4)	45	11.4	3.7	11.4 (8.0-14.2)
Hammersmith	52	19.6	5.4	18.8 (15.2-24.2)	7	15.8	3.3	16.8 (13.7-18.0)
Leicester	40	12.2	5.2	10.7 (8.1-16.5)	0	-	-	-
Manchester	116	14.7	4.4	14.0 (11.7-17.4)	50	13.9	4.4	13.4 (10.7-17.2)
Sheffield	26	15.8	4.7	15.4 (13.4-16.6)	15	13.7	4.9	13.5 (12.2-17.0)
Portsmouth	37	15.1	3.4	15.1 (13.2-18.0)	11	14.1	4.7	16.7 (10.7-17.1)
Birmingham	22	17.6	7.0	15.3 (12.3-23.8)	8	14.1	5.1	12.5 (9.9-18.6)
Edinburgh	58	12.4	3.9	11.2 (9.3-15.6)	23	8.9	3.1	7.2 (6.6-11.6)
Liverpool	43	16.4	4.8	16.5 (14.0-18.5)	43	13.0	4.0	12.4 (10.8-16.2)
Bristol	31	13.6	2.8	13.7 (11.5-14.8)	22	14.6	2.5	14.2 (13.3-16.0)
St George's	41	11.9	3.6	11.6 (9.1-14.8)	17	11.4	3.6	12.5 (9.5-13.2)
Leeds	57	14.7	4.6	14.0 (12.0-16.2)	57	13.9	3.3	13.9 (11.6-16.2)
The Royal Free	46	13.1	3.9	13.1 (10.6-15.7)	36	11.5	2.2	11.5 (9.9-12.6)
The Royal London	32	14.2	5.1	14.0 (9.8-17.4)	28	11.7	3.4	11.0 (9.0-13.9)
Coventry	11	16.8	6.3	14.8 (11.3-22.3)	2	11.5	4.6	11.5 (8.2-14.7)
Cardiff	39	13.6	3.7	12.8 (10.8-16.0)	70	12.7	4.5	11.9 (9.2-16.3)
Glasgow	72	13.8	4.1	14.7 (10.5-16.4)	31	10.2	4.3	8.7 (6.5-13.0)



**Figure 3.8 Mean cold ischaemia time for DBD and DCD donor kidney transplants in each transplant centre**



**Figure 3.9 Median cold ischaemia time for DBD and DCD donor kidney transplants in each transplant centre**



### **3.4.3 Timing of dispatch of donor blood for tissue typing in relation to duty office notification of potential donor**

Once a donor is identified, donor pre-retrieval peripheral blood is dispatched to H&I laboratory for tissue typing (TT). There was wide variation in the time interval between dispatching of the donor blood and notification of donor to duty office (donor notification) for both DBD and DCD donors. In the case of DBD donors, the timing of donor notification ranged from 47.5 hours before dispatching of donor blood for TT to 26.1 hours after. For DCD donors, it ranged from 57.5 hours before dispatching of donor blood for TT to 18.0 hours after.

### **3.4.4 Donor HLA typing time**

The mean time interval between donor blood sample dispatched for tissue typing (TT) and HLA data received by Duty Office (DO) (TT time) was 6.8 hours (SD 4.0).

### **3.4.5 Timing of retrieval surgery**

There was a significant difference between the timing of retrieval surgery in relation to completion of the match run between DBD and DCD donors ( $F=179.886$ ,  $p<0.0001$ ). On average, retrieval surgery started 5.7 hours (SD 3.9) after the match run was completed for DBD donors and 2.0 hours (SD 4.2) after for DCD donors. In both groups, some retrieval operations started before the match runs were completed; 27 DBDs and 124 DCDs retrievals started before match run was completed.

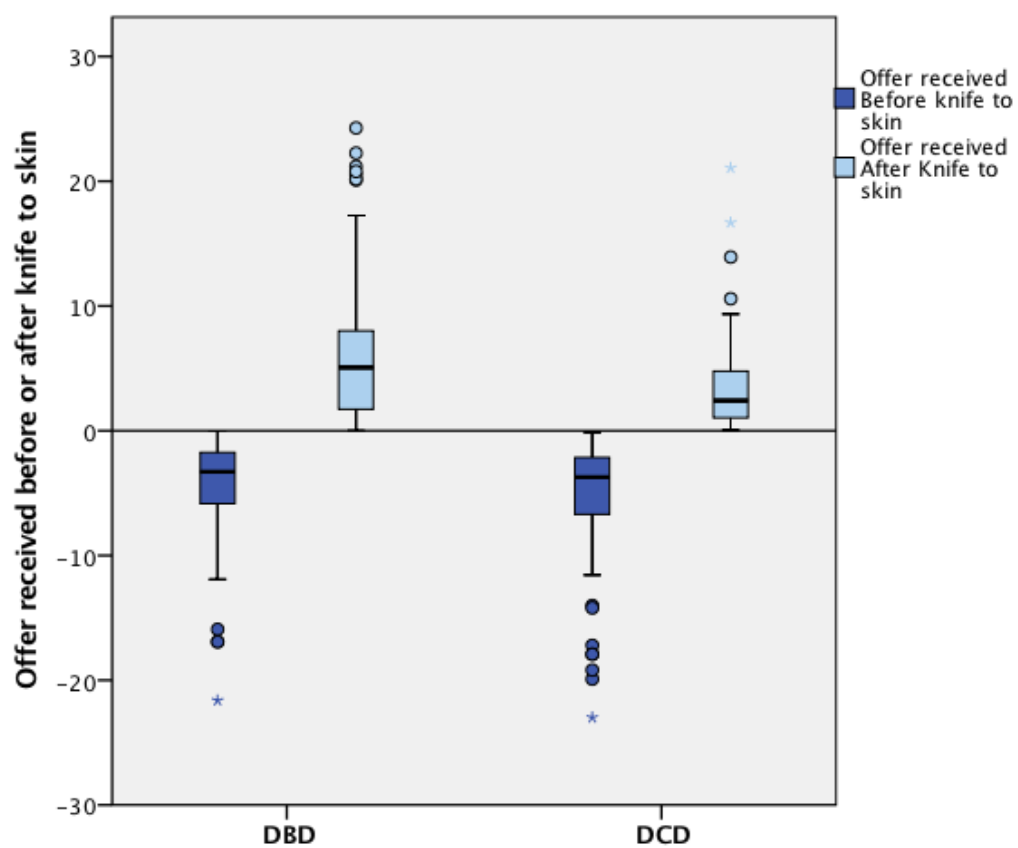
#### **3.4.6 Timing of start of retrieval surgery (knife to skin) and kidney in ice box**

The interval between knife to skin and kidney in the ice box was a mean of 1.31 hours (SD 0.46) with the minimum interval of 0.18 hours (11 minutes) and the maximum of 3.68 hours (221 minutes). There was no significant difference in the time interval for DBD and DCD donors (Mean 1.31 hours and 1.29 hours, SD 0.43 and 0.49, respectively) ( $F=1.218$ ,  $p=0.270$ )

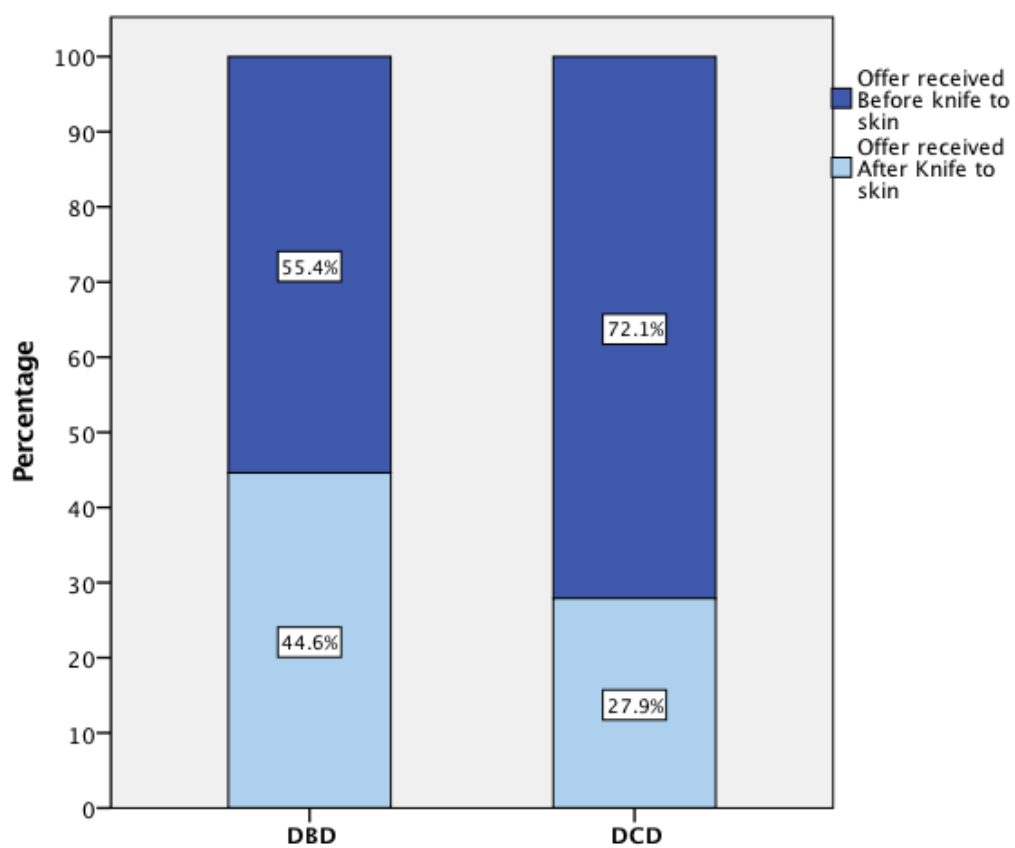
#### **3.4.7 Timing of kidney offer in relation to retrieval surgery**

There was a significant difference in the timing of offer for DBD and DCD kidneys ( $F=11.826$ ,  $p=0.001$ ), with a large proportion of DCD kidneys being offered before the start of retrieval (72.1% vs 55.4%) but the impact of donor type on CIT in the two offer groups was not significantly different. (Figures 3.10, 3.11)

**Figure 3.10 Timing of kidney offer in relation to start of retrieval surgery in DBD and DCD donor kidney transplants**



**Figure 3.11 DBD and DCD kidney offer in relation to start of transplantation surgery (knife to skin)**



Timing of offer significantly impacted on CIT, with organs that were offered at or before start of retrieval surgery having shorter CIT as compared to those offered after start of retrieval surgery. There was more than 2 hours' difference in CIT between the two groups ( $p<0.0001$ ). (Table 3.11, Figure 3.12)

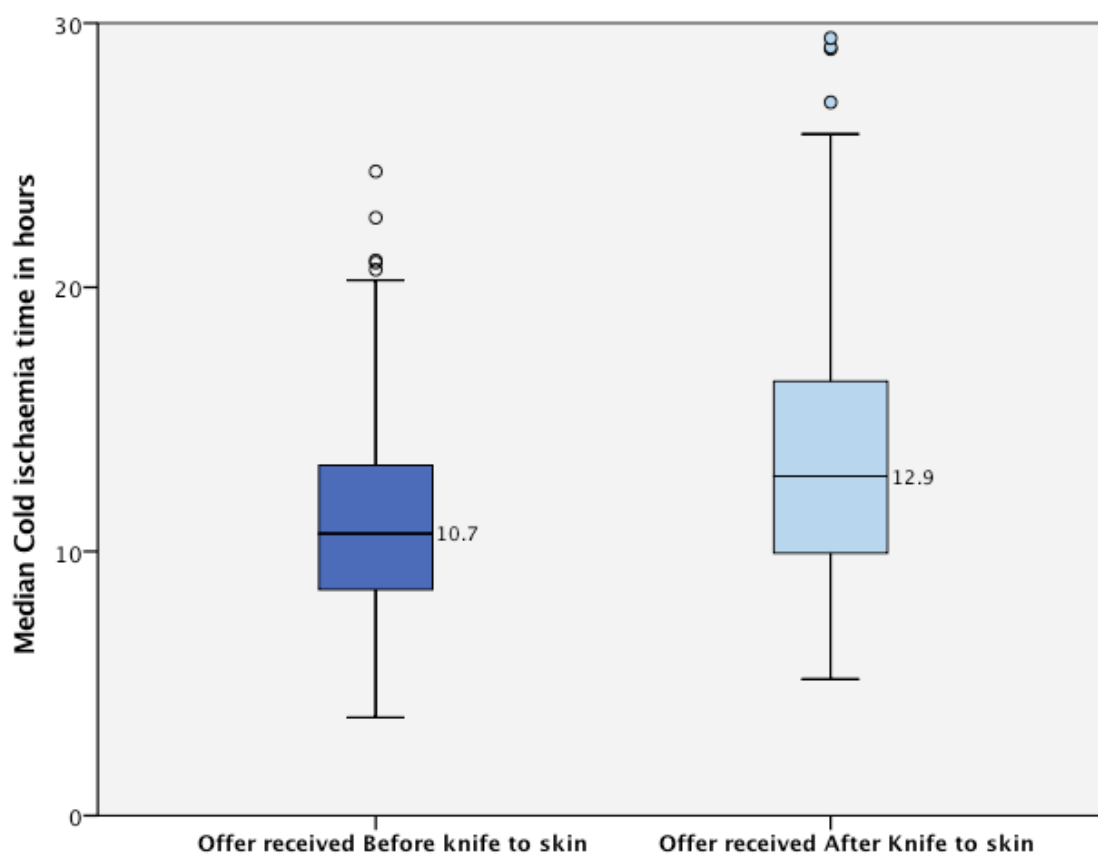
The timing of offer was significant for DBD kidneys ( $F=25.024$ ,  $p=0.0001$ ) but not for DCD kidneys ( $F=3.200$ ,  $p=0.076$ ) (Figure 3.13)

**Table 3.11 Timing of kidney offer and impact on cold ischaemia time**

Timing of offer	n	CIT in hours				
		Mean	SD	Minimum	Maximum	Median (IQ Range)
Before knife to skin	247	11.3	3.9	3.7	24.4	10.7 (8.6-13.3)
After knife to skin	147	13.7	5.0	5.2	29.4	12.9 (9.9-16.5)

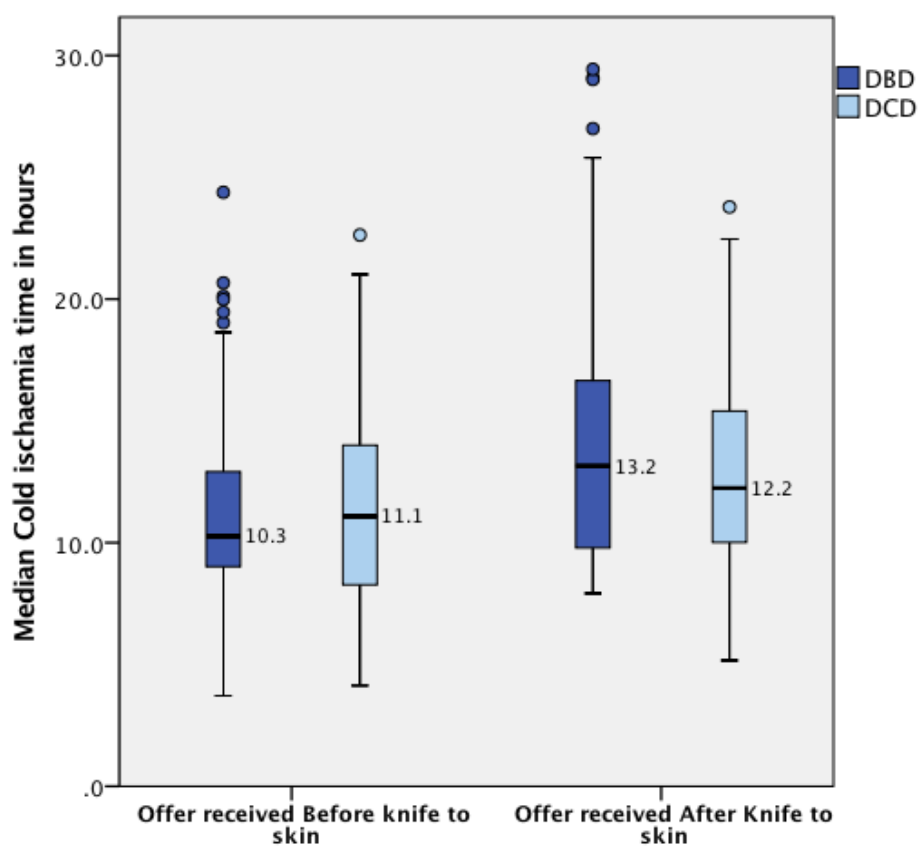
Significance:  $F=26.328$ ,  $p<0.0001$

**Figure 3.12 Impact of timing of knife to skin in relation to kidney offer on cold ischaemia time**





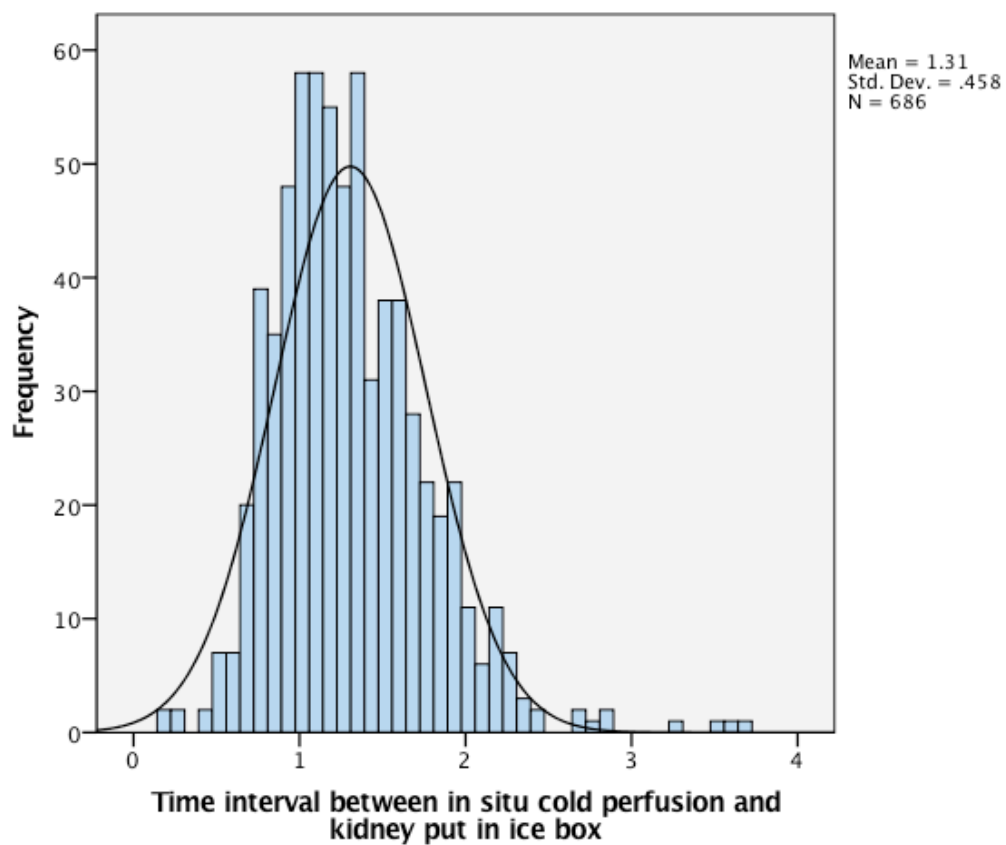
**Figure 3.13 Impact of timing of DBD and DCD kidney offer in relation to retrieval surgery on cold ischaemia time**



### 3.4.8 Timing of kidney in ice box in relation to in situ cold perfusion at retrieval surgery

The data were available for 686 kidneys. The median time interval was 1.3 hours (IQR 1.0-1.6). (Figure 3.14)

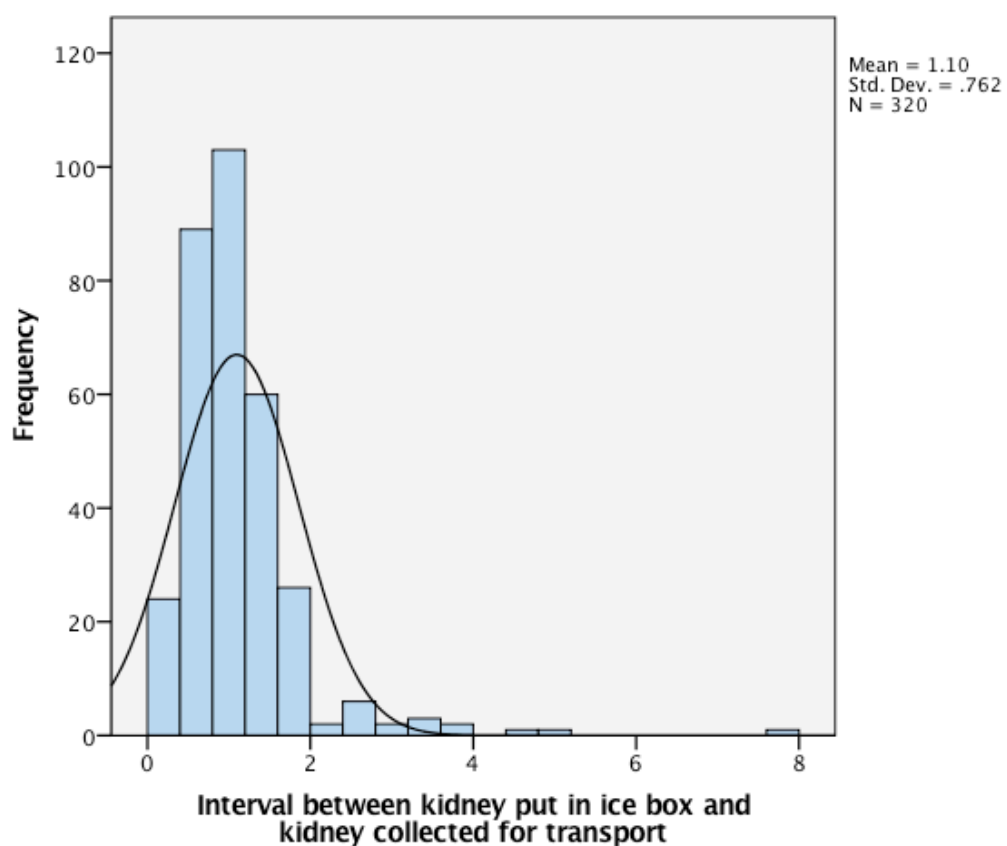
**Figure 3.14** Timing of kidney in ice box in relation to in situ cold perfusion at retrieval surgery



### 3.4.9 Timing of kidney collection in relation to kidney put in ice box

The data were available for only 320 kidneys. Median time interval between kidney put in ice box and kidney collected for transport was 1.0 hour (IQR 0.7-1.3). (Figure 3.15)

**Figure 3.15** Timing of kidney collection in relation to kidney put in ice box



### **3.5 Transport Factors and impact on cold ischaemia time**

Sixty-seven percent of the kidneys for transplant were imported from a different centre, thus requiring use of transport facilities to ship kidneys. Transport data were available for all 1137 imported kidneys.

#### **3.5.1 Kidney travel distance**

Kidneys for transplants were grouped into 6 categories according to the distance travelled from donor hospital to recipient transplant centre which was calculated as the straight line between the centres using GoogleMaps.

Group 1: In-house

Group 2: Under 20 miles

Group 3: 20-50 miles

Group 4: 50-100 miles

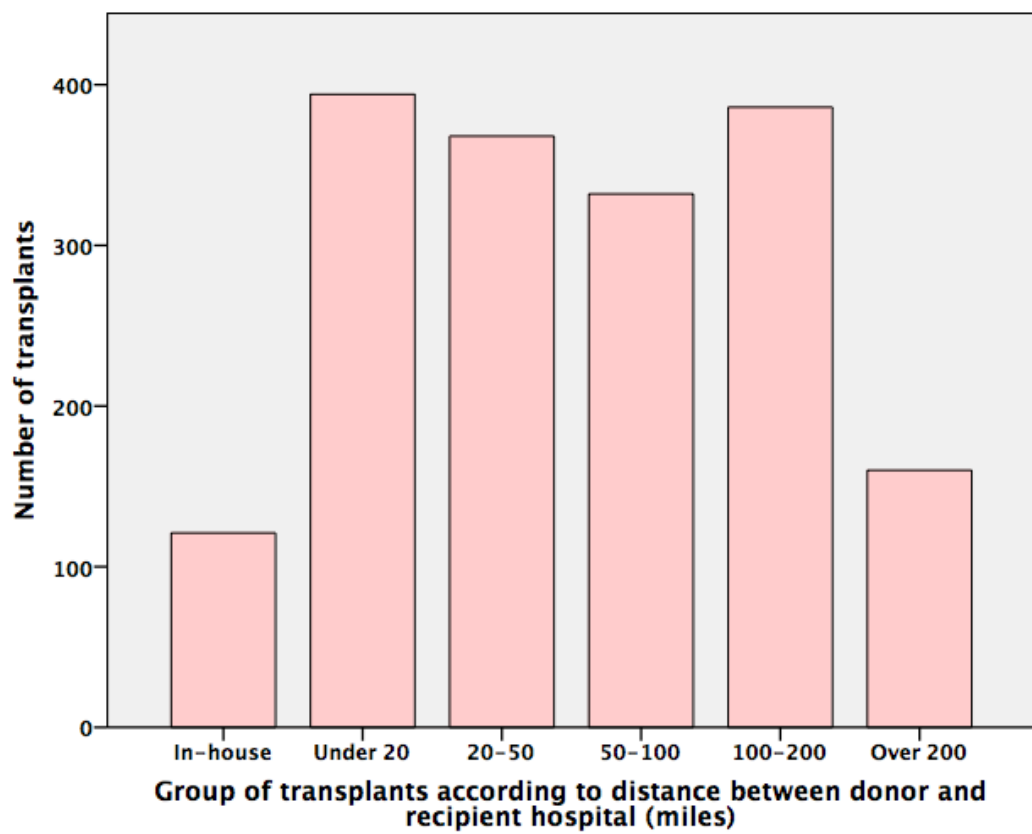
Group 5: 100-200 miles

Group 6: Over 200 miles

There was a wide variation in distance travelled by retrieved kidneys from 122 donor hospitals to 22 transplant centres ranging from 0 to 658 miles (mean 79.9 miles).

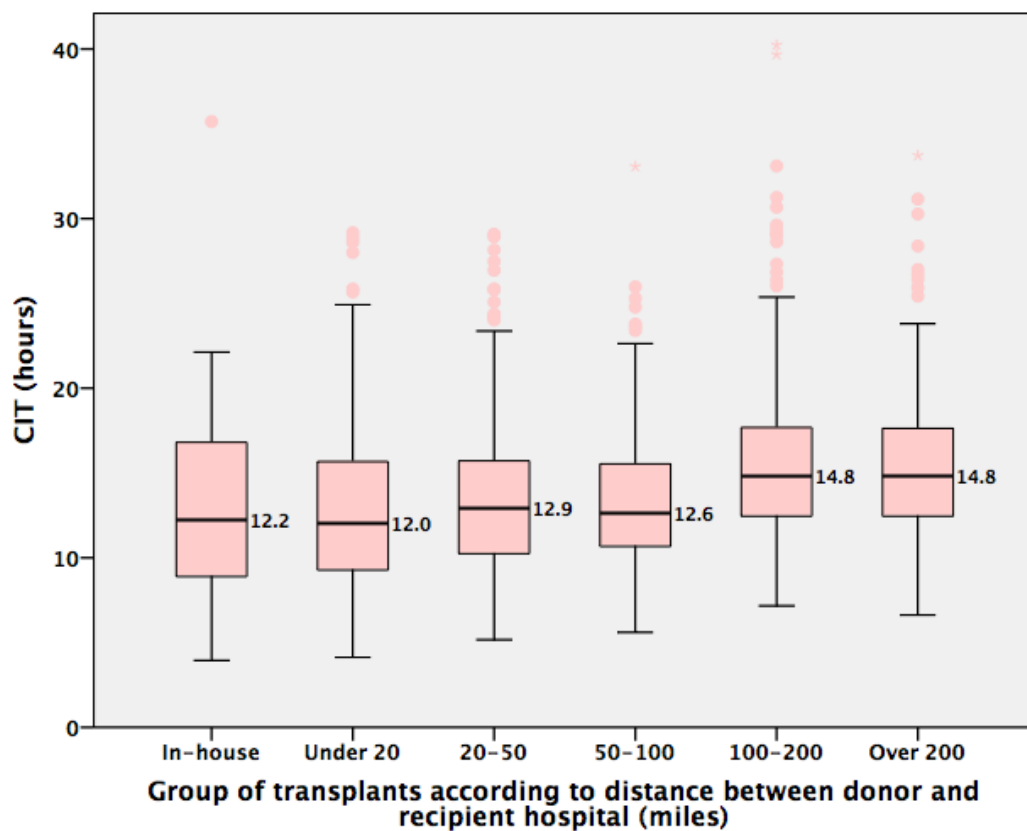
(Figure 3.16)

**Figure 3.16 Number of transplants in relation to distance between donor hospital and recipient transplant centre in miles**



There was a positive correlation between the groups of distance travelled by kidneys and their CIT; this was significant when the distance was above 100 miles. (Figure 3.17)

**Figure 3.17 Impact of travel distance between donor hospital and recipient transplant centre on cold ischaemia time**

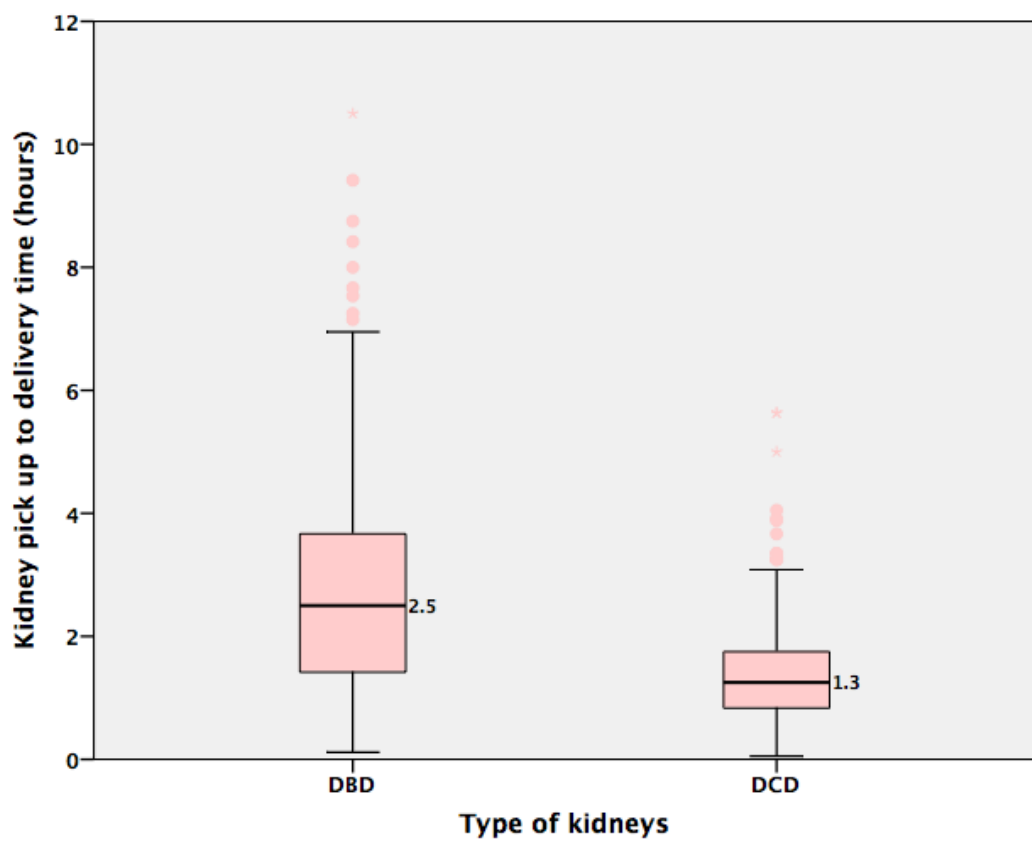


Significance:  $F=22.966$ ,  $p<0.0001$

### **3.5.2 Variation in travel time and distance for DBD and DCD kidneys**

The data for kidney collection and delivery time (kidney travel time) were available for 67% of imported kidneys. It took an average of an hour for kidneys to be collected by transport personnel after they were put in ice box. Distance travelled by DBD kidneys was considerably longer (median 95.9 miles) with longer travel time (median 2.5 hours) than DCD kidneys (median 23.5 miles and median 1.3 hours, respectively). (Figures 3.18, 3.19)

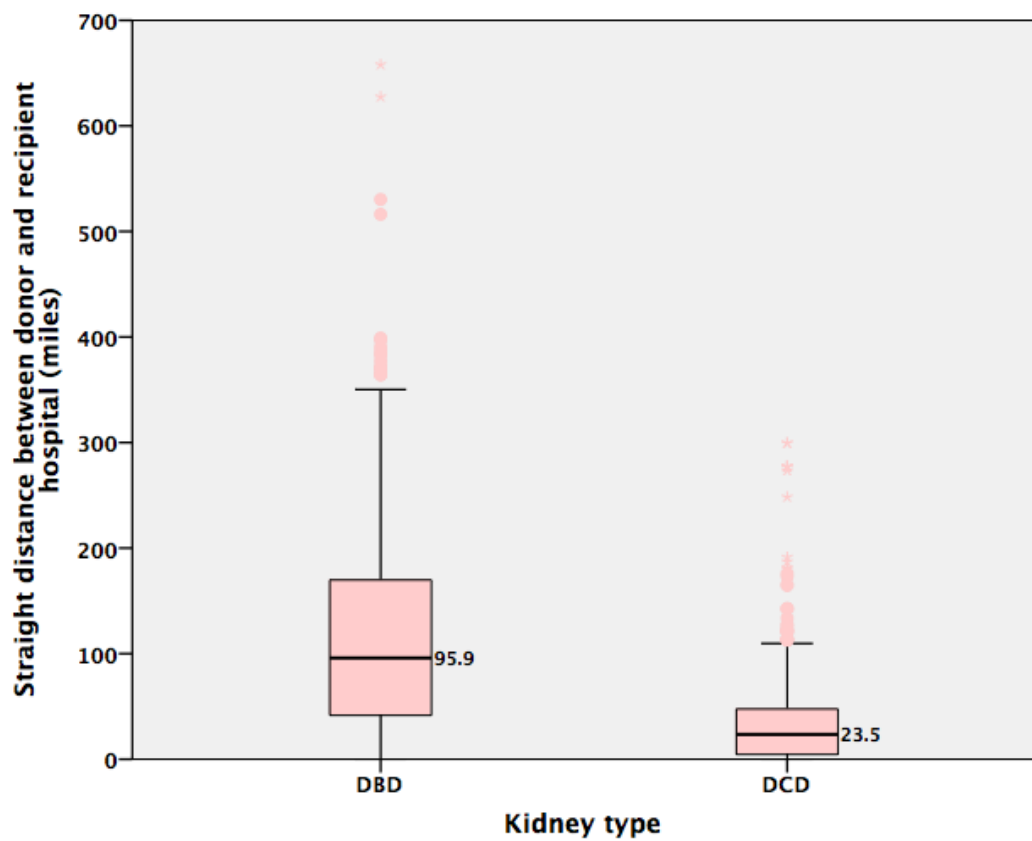
**Figure 3.18 Kidney collection to delivery time (kidney travel time) for DBD and DCD kidneys**



Significance:  $F=98.759$ ,  $p<0.0001$



**Figure 3.19 Distance between donor hospital and recipient transplant centre for transport of DBD and DCD kidneys**



Significance:  $F=448.056$ ,  $p<0.0001$

### **3.5.3 Mode of transport of kidneys**

The data for mode of transport for imported kidneys were available for 544 kidneys (48%). The kidneys were grouped according to their mode of transport of as follows:

Road

Road and blue-lighted

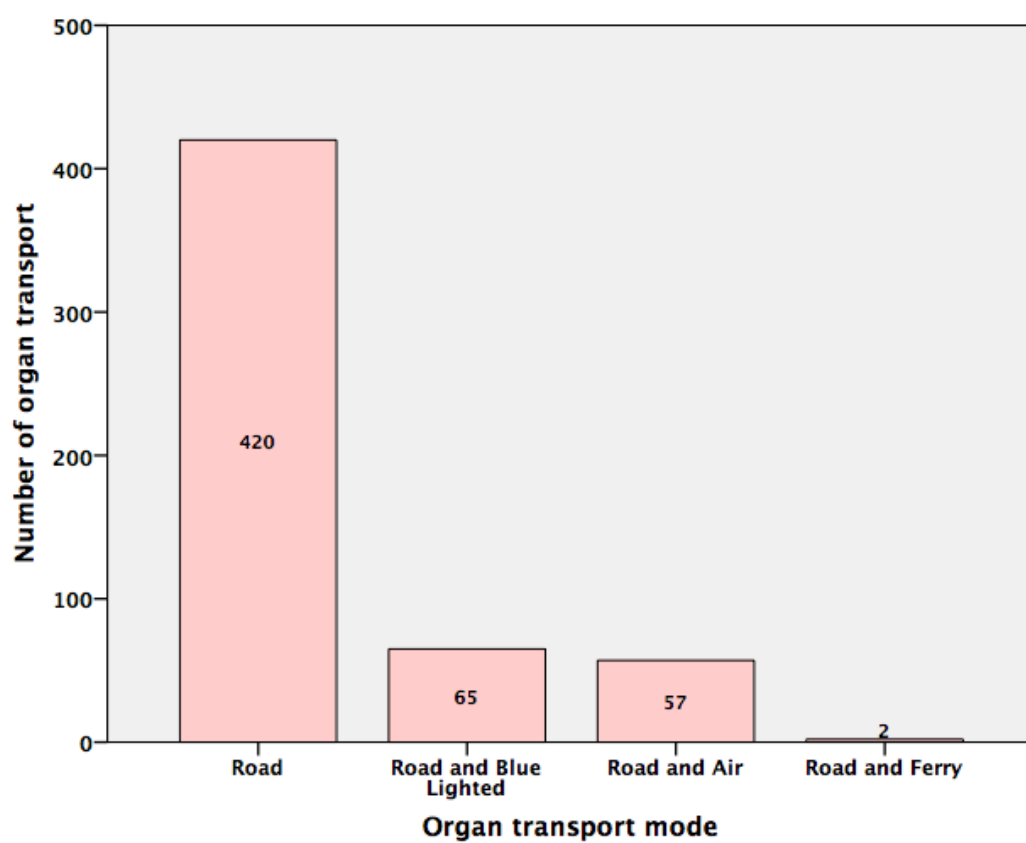
Road and air

Road and ferry

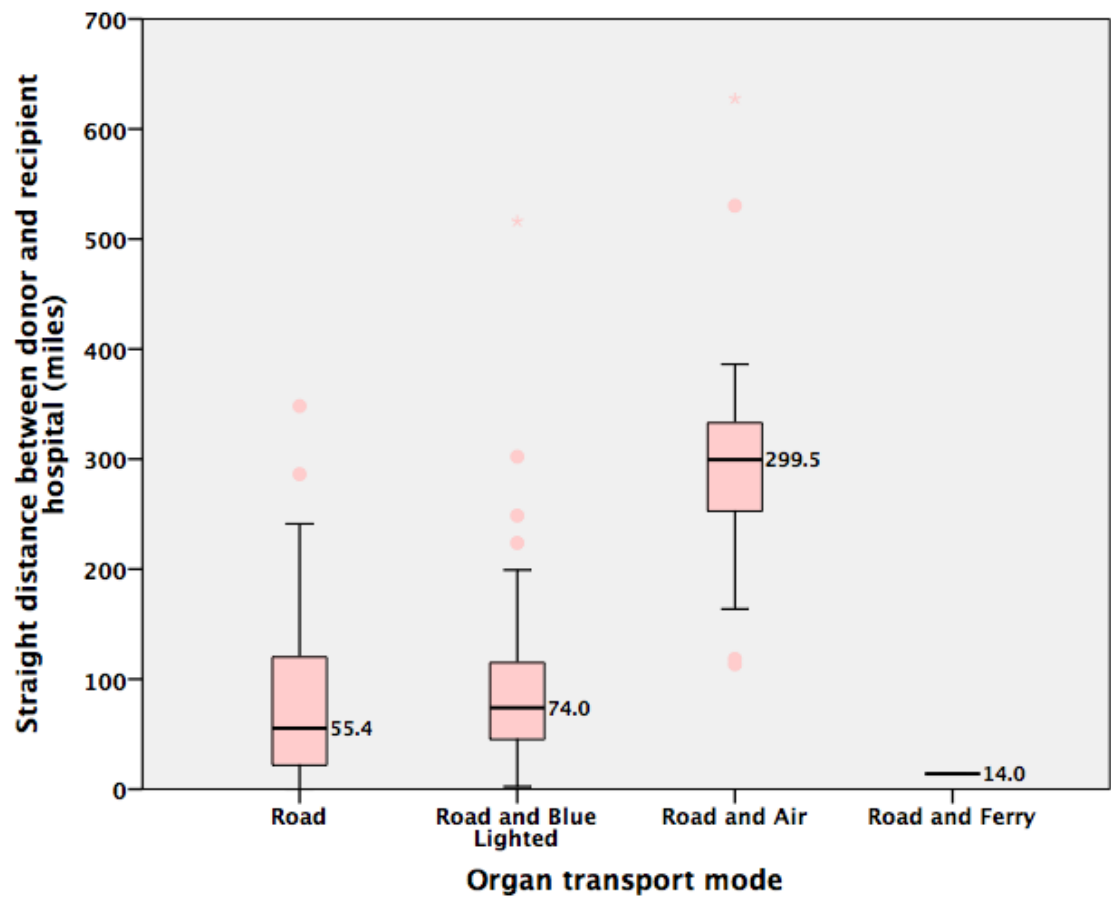
Majority (420) of kidneys travelled by road, 65 were transported by road and blue lighted, 57 by air and 2 by ferry. (Figure 3.20)

Of the 4 categories of transport kidneys transported by air travelled the furthest distance (median 299.5 miles) and had the longest travel time (median 4.1 hours). (Figures 3.21, Figure 3.22)

**Figure 3.20 Mode of transport of kidneys**

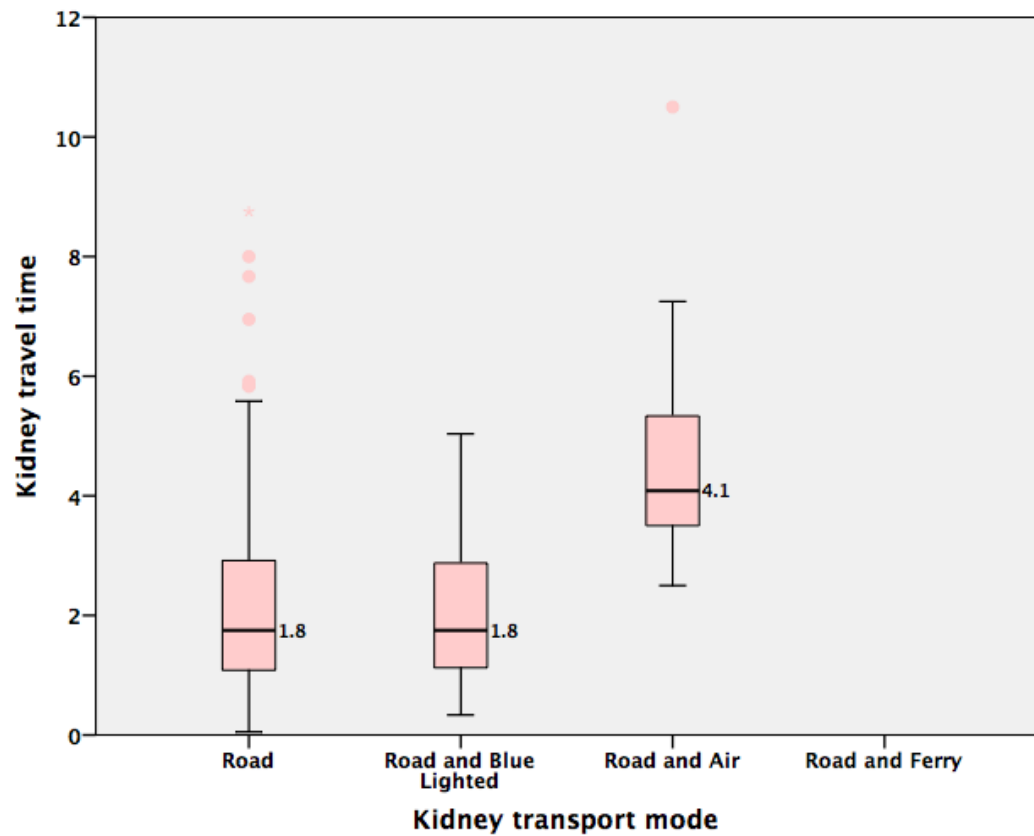


**Figure 3.21 Distance travelled by kidneys and the mode of transport**



Significance:  $F=176.842$ ,  $p=0.0001$

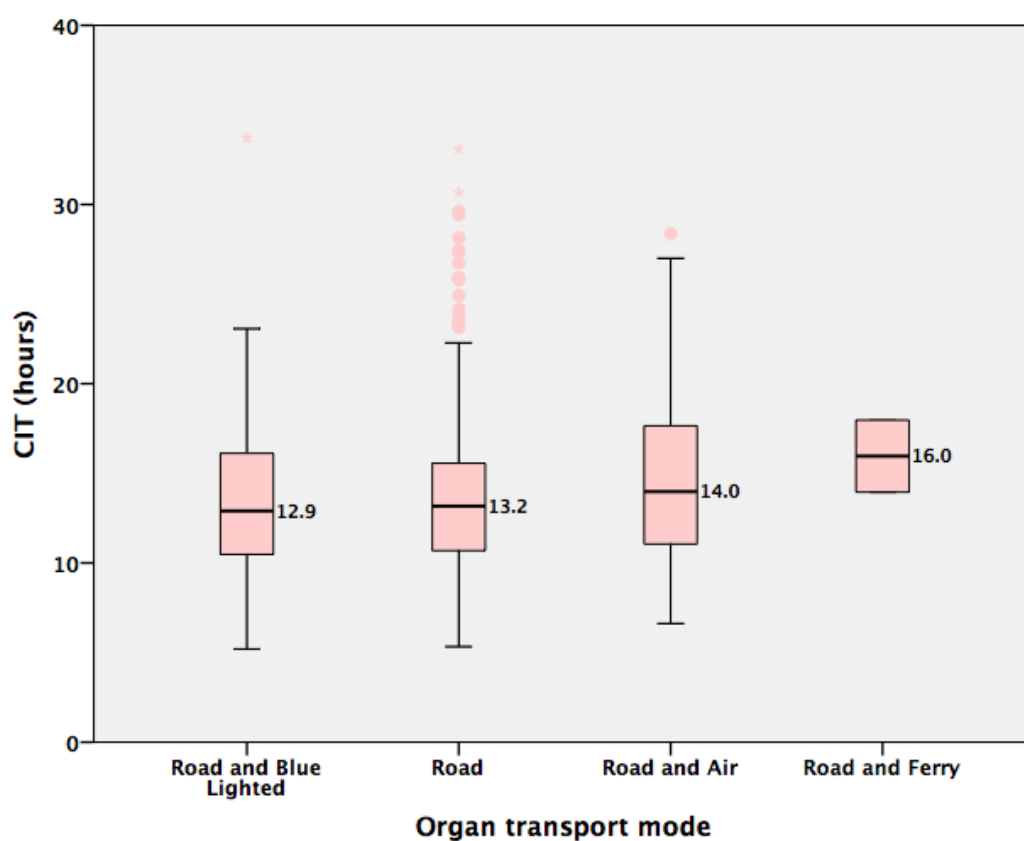
**Figure 3.22 Kidney travel time and mode of transport**



Significance:  $F=35.379$ ,  $p<0.0001$

However, CIT for kidneys transported by air were not significantly different than for those transported via road only, whether blue lighted or not. (Figure 3.23)

**Figure 3.23 Impact of mode of transport of kidneys on cold ischaemia time**



Significance:  $F=2.420$ ,  $p=0.065$

### 3.6 H&I factors and impact on cold ischaemia time

#### 3.6.1 Crossmatching

The majority of the transplants were performed following a prospective pre-transplant crossmatching (pXM) to establish HLA compatibility between donor and recipient (63.9%). A third of the transplants were performed with a virtual crossmatch (vXM), without the need for a pre-transplant crossmatching (36.1%). (Table 3.12)

**Table 3.12 Number transplants with pre-transplant crossmatch (pXM) and virtual crossmatch (vXM)**

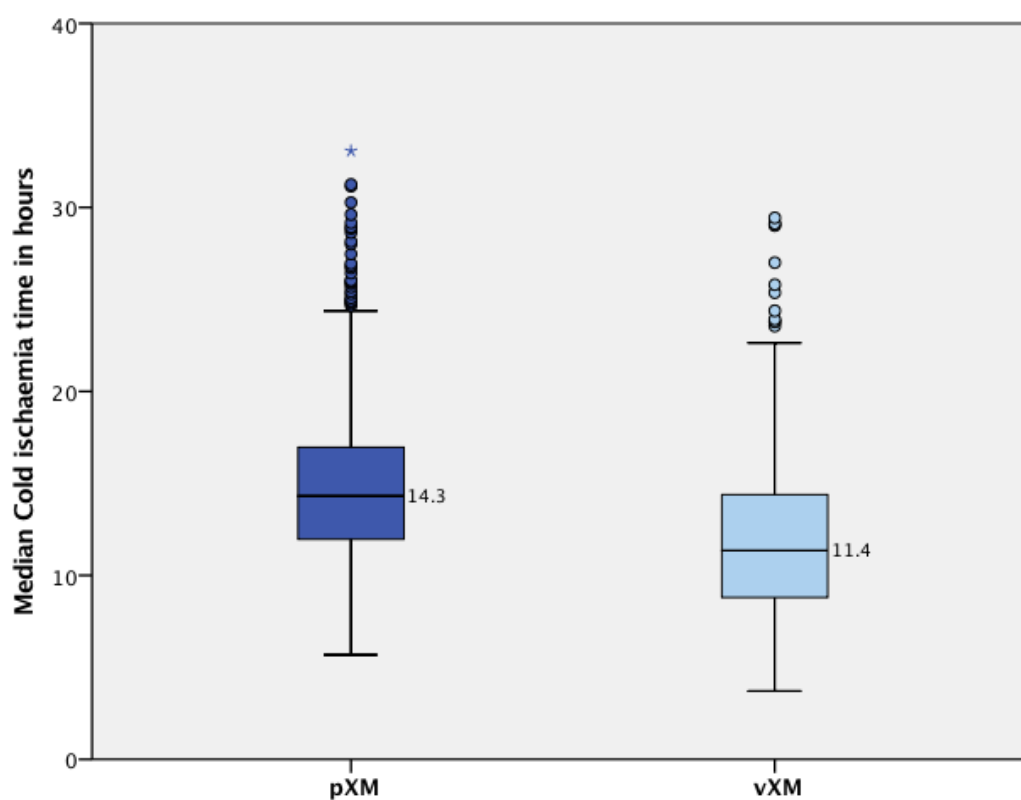
<b>XM</b>	<b>n (%)</b>
pXM	1127 (63.9)
vXM	636 (36.1)
Total	1763 (100)

There was a significant difference in CIT between the pXM and vXM groups, which approached 3 hours ( $F=204.066$ ,  $p<0.0001$ ). (Table 3.13, Figure 3.24)

**Table 3.13 Impact of type of crossmatch on cold ischaemia time**

XM	CIT (hours)	
	Mean (SD)	Median (IQR)
pXM	14.8 (4.2)	14.3 (12.0-17.0)
vXM	12.0 (4.4)	11.4 (8.8-14.4)

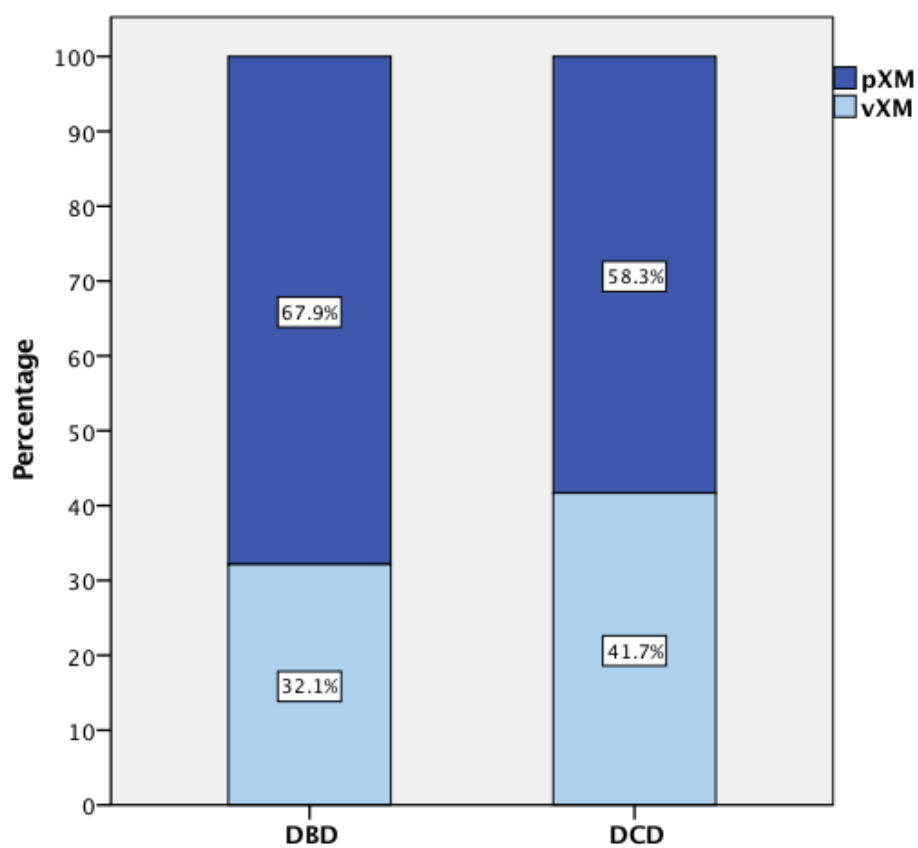
**Figure 3.24 Impact of type of crossmatch on cold ischaemia time**





The majority of both DBD and DCD kidney transplants was performed following pXM, although a higher proportion of DCD kidney transplants was performed with a vXM than DBD kidney transplants (41% and 32.1%, respectively). (Figure 3.25)

**Figure 3.25 Type of crossmatch for DBD and DCD kidney transplants**



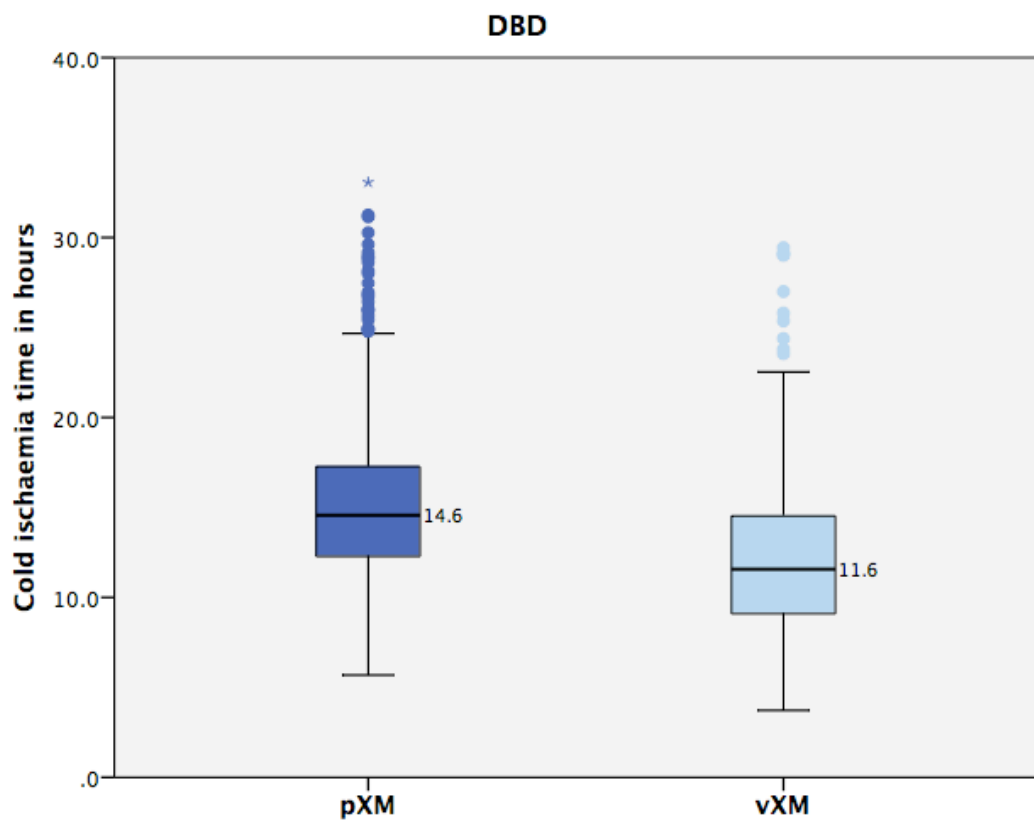
### 3.6.2 Type of crossmatching for DBD and DCD kidney transplants

CIT was significantly shorter when transplants proceeded with a vXM for both DBD and DCD transplants than when they required a pXM. Median CIT was 3.0 hours and 2.8 hours shorter for DBD and DCD transplants, respectively, for vXM group. (Table 3.14, Figures 3.26, 3.27)

**Table 3.14 Impact of crossmatch on cold ischaemia time for DBD and DCD kidney transplants**

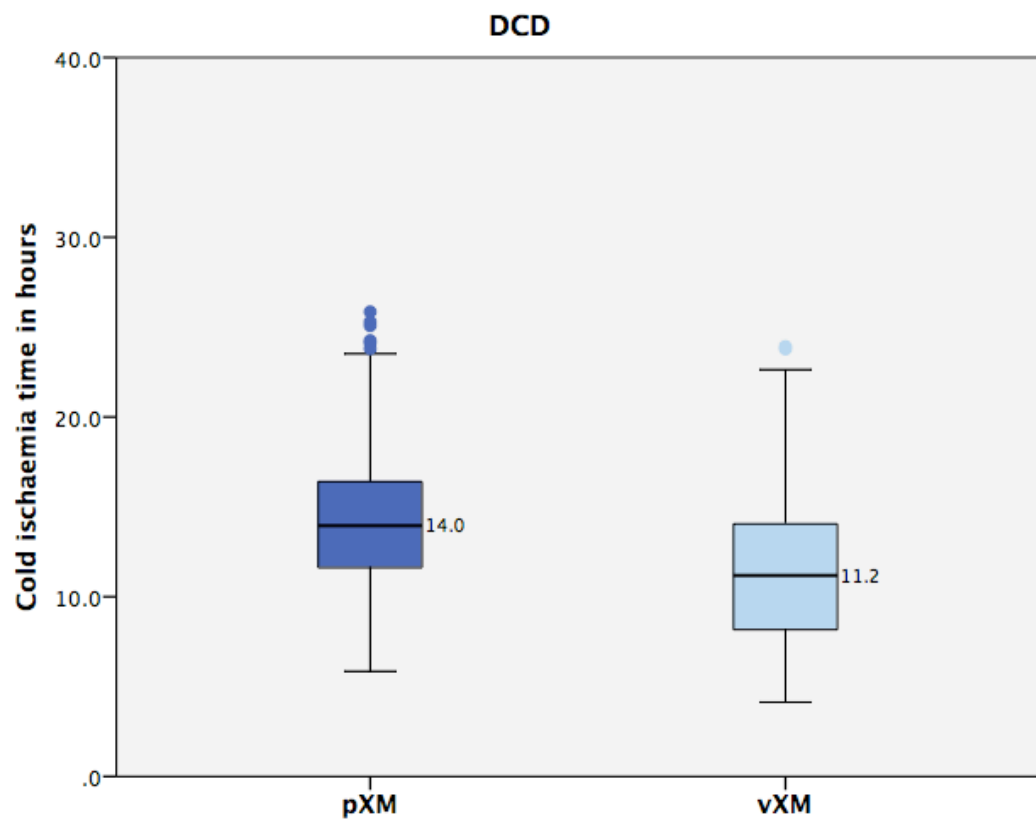
XM	DBD		DCD	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
pXM	15.2(4.4)	14.6 (12.3-17.3)	14.1 (3.8)	14.0 (11.6-16.5)
vXM	12.4 (4.6)	11.6 (9.1-14.5)	11.5 (4.2)	11.2 (8.2-14.1)

**Figure 3.26 Impact of pXM and vXM on cold ischaemia time for DBD kidney transplants**



Significance:  $F=115.478$ ,  $p<0.0001$

**Figure 3.27 Impact of pXM and vXM on cold ischaemia time for DCD kidney transplants**



Significance:  $F=77.086$ ,  $p<0.0001$

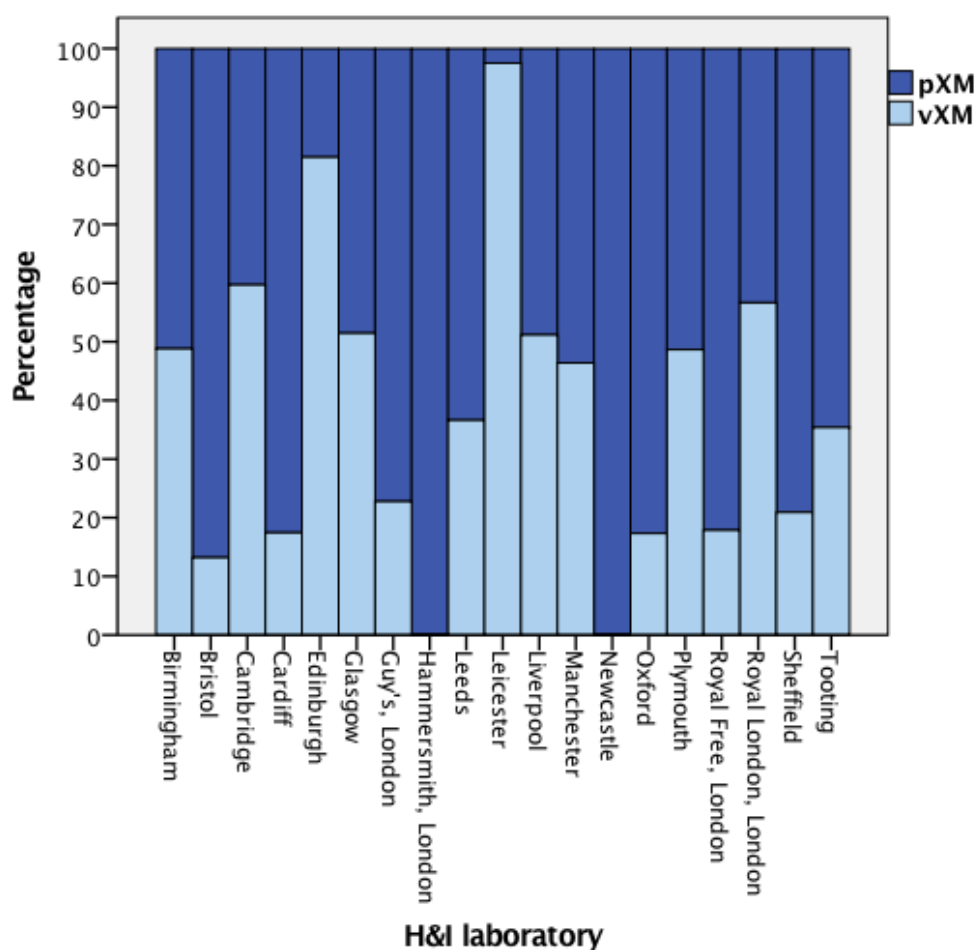
### 3.6.3 H&I laboratory variation in type of crossmatching

There was a wide variation in crossmatching policy across the H&I laboratories.

Two of the laboratories, Hammersmith and Newcastle, did not have a vXM policy.

Leicester performed 99% of their transplants with a vXM. (Figure 3.28, Table 3.15)

**Figure 3.28 H&I laboratory variation in crossmatching policy**

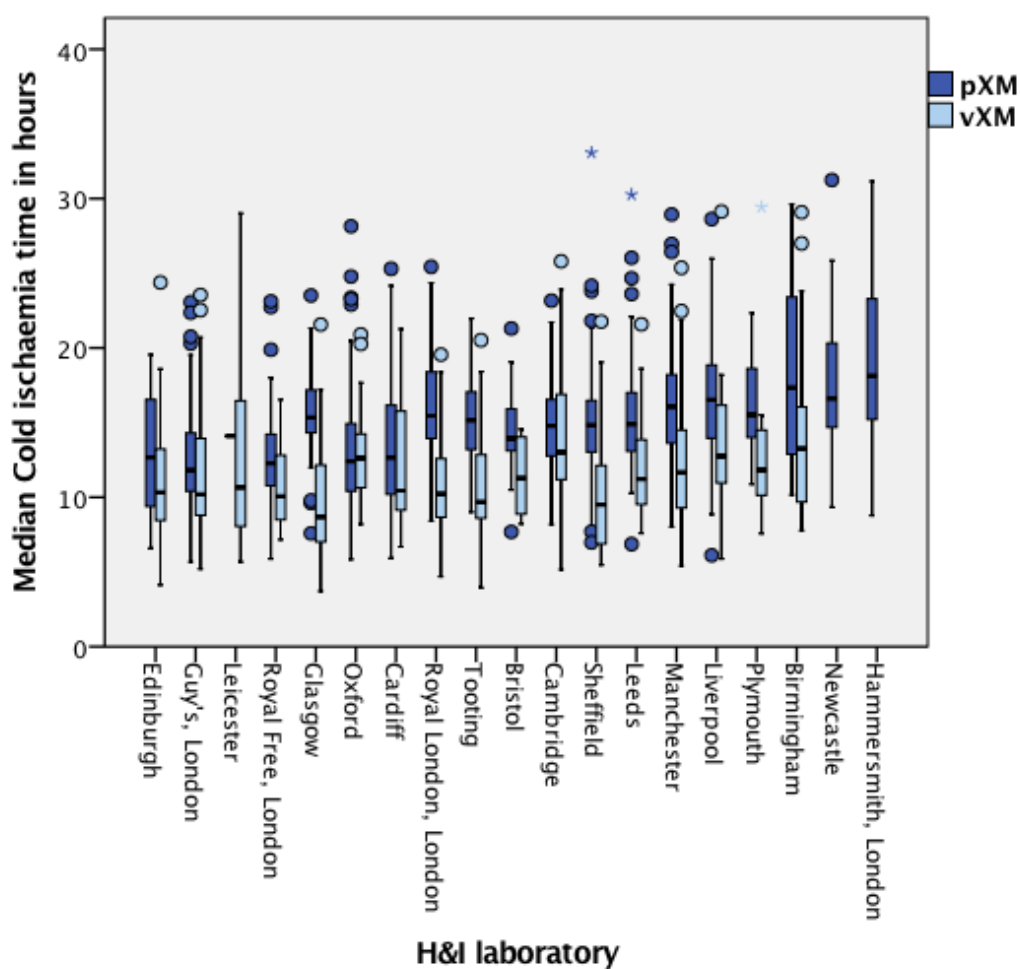


**Table 3.15 H&I laboratory variation in crossmatching policy**

<b>H&amp;I Laboratory</b>	<b>pXM (%)</b>	<b>vXM (%)</b>	<b>Total</b>
Birmingham	22 (51.2)	21 (48.8)	43
Bristol	46 (86.8)	7 (13.2)	53
Cambridge	56 (40.3)	83 (59.7)	139
Cardiff	90 (82.6)	19 (17.4)	109
Edinburgh	15 (18.5)	66 (81.5)	81
Glasgow	50 (48.5)	53 (51.5)	103
Guy's, London	122 (77.2)	36 (22.8)	158
Hammersmith, London	59 (100)	0	59
Leeds	71 (63.4)	41 (36.6)	112
Leicester	1 (2.5)	39 (97.5)	40
Liverpool	42 (48.8)	44 (51.2)	86
Manchester	89 (53.6)	77 (46.4)	166
Newcastle	66 (100)	0	66
Oxford	129 (82.7)	27 (17.3)	156
Plymouth	19 (51.4)	18 (48.6)	37
Royal Free, London	69 (82.1)	15 (17.9)	84
Royal London, London	26 (43.3)	34 (56.7)	60
Sheffield	102 (79.1)	27 (20.9)	129
Tooting	53 (64.6)	29 (35.4)	82

There was a significant difference in median CIT between pXM and vXM transplants for each H&I laboratory. All kidney transplants that proceeded with a vXM had a shorter median CIT in each H&I laboratory. (Figure 3.29, Table 3.16)

**Figure 3.29 Impact of H&I laboratory variation in crossmatching policy on cold ischaemia time**



Significance:  $F = 4.404$ ,  $p < 0.0001$

**Table 3.16 Cold ischaemia time for kidney transplants with pXM and vXM in each H&I laboratory**

H&I Laboratory	CIT (Hours)	XM	
		pXM	vXM
Birmingham	Mean (SD)	18.5 (6.1)	14.4 (6.2)
	Median (IQR)	17.3 (12.9-23.4)	13.3(9.7-16.1)
Bristol	Mean (SD)	14.3 (2.5)	11.4 (2.6)
	Median (IQR)	13.9 (13.1-15.9)	11.3 (8.9-14.0)
Cambridge	Mean (SD)	14.8 (3.2)	13.7 (4.4)
	Median (IQR)	14.8 (12.8-16.6)	13.0 (11.2-16.9)
Cardiff	Mean (SD)	13.2 (4.2)	12.3 (4.6)
	Median (IQR)	12.7 (10.1-16.3)	10.5 (9.1-15.8)
Edinburgh	Mean (SD)	13.0 (4.4)	11.2 (3.9)
	Median (IQR)	12.7 (9.1-17.8)	10.3 (8.5-13.2)
Glasgow	Mean (SD)	15.7 (3.0)	9.9 (3.7)
	Median (IQR)	15.3 (14.3-17.2)	8.7 (7.0-12.2)
Guy's, London	Mean (SD)	12.3 (3.5)	11.5 (4.8)
	Median (IQR)	11.8 (10.4-14.3)	10.2 (8.8-13.9)
Hammersmith, London	Mean (SD)	19.2 (5.3)	-
	Median (IQR)	18.1 (15.2-23.3)	-
Leeds	Mean (SD)	15.6 (4.0)	12.1 (3.5)
	Median (IQR)	14.9 (13.1-17.0)	11.2 (9.5-13.9)
Leicester	Mean (SD)	14.1 (-)	12.1 (5.3)
	Median (IQR)	14.1 (14.1-14.1)	10.7 (8.1-16.5)
Liverpool	Mean (SD)	16.4 (4.4)	13.1 (4.5)
	Median (IQR)	16.5 (14.0-18.9)	12.8 (10.8-16.2)
Manchester	Mean (SD)	16.3 (3.8)	12.3 (4.2)
	Median (IQR)	16.1 (13.6-18.2)	11.7 (9.3-14.5)
Newcastle	Mean (SD)	17.5 (4.4)	-
	Median (IQR)	16.6 (14.6-20.4)	-
Oxford	Mean (SD)	13.1 (3.8)	12.9 (3.3)
	Median (IQR)	12.4 (10.4-14.9)	12.6 (10.1-14.5)
Plymouth	Mean (SD)	16.1 (3.2)	13.6 (6.1)
	Median (IQR)	15.5 (14.0-18.6)	11.8 (10.1-14.5)
Royal Free, London	Mean (SD)	12.8 (3.3)	10.6 (3.0)
	Median (IQR)	12.3 (10.8-14.3)	10.1 (8.3-13.3)
Royal London, London	Mean (SD)	16.1 (4.3)	10.7 (3.3)
	Median (IQR)	15.5 (13.9-18.4)	10.2 (8.7-12.6)
Sheffield	Mean (SD)	15.1 (3.8)	10.6 (4.6)
	Median (IQR)	14.8 (13.0-16.6)	9.5 (6.9-12.1)
Tooting	Mean (SD)	15.3 (2.8)	10.7 (4.2)
	Median (IQR)	15.2 (13.2-17.1)	9.7 (8.6-12.9)

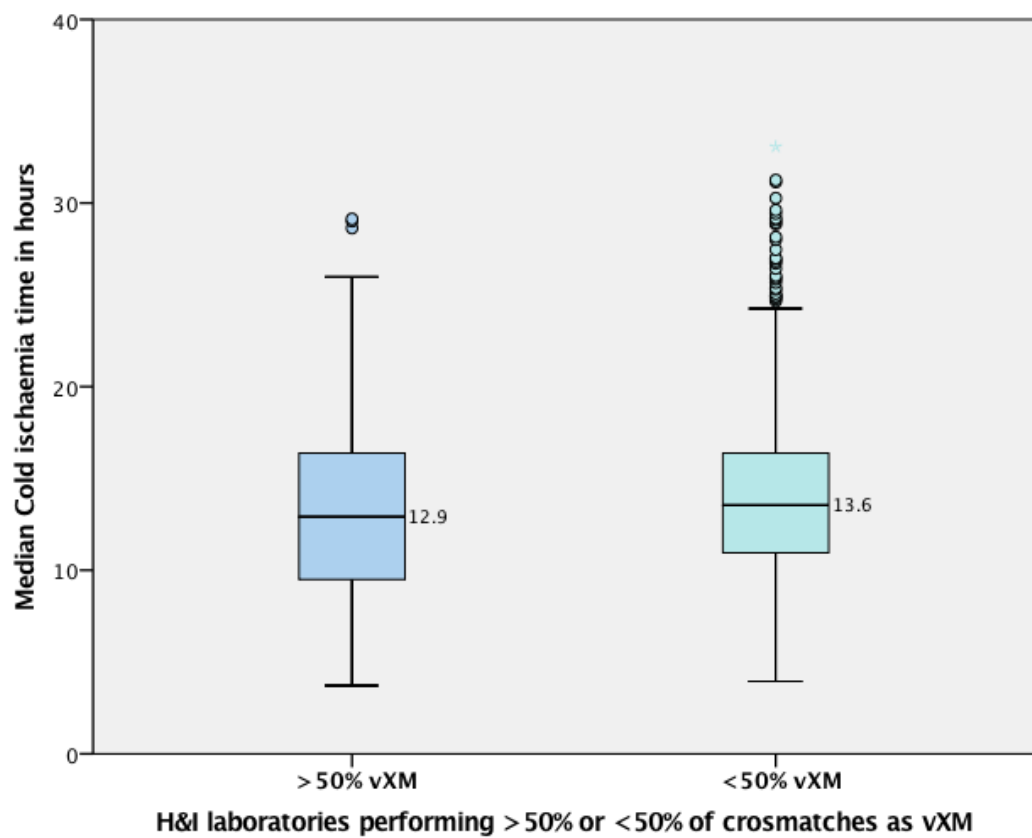


### **3.7 Virtual crossmatch**

A third (n=636) of the total transplants went ahead with a vXM (Table: 3.12). Of the 19 H&I laboratories, only 8 approved vXM in greater than half of their transplants.

There was almost an hour's difference in median CIT between the 8 H&I laboratories that approved for a transplant to go ahead with a vXM in >50% of their transplants and the 11 that approved for it in <50% of their transplants (Figure 3.30).

**Figure 3.30 Median cold ischaemia time for H&I laboratories that perform vXM in more than 50% or less than 50% of kidney transplants**

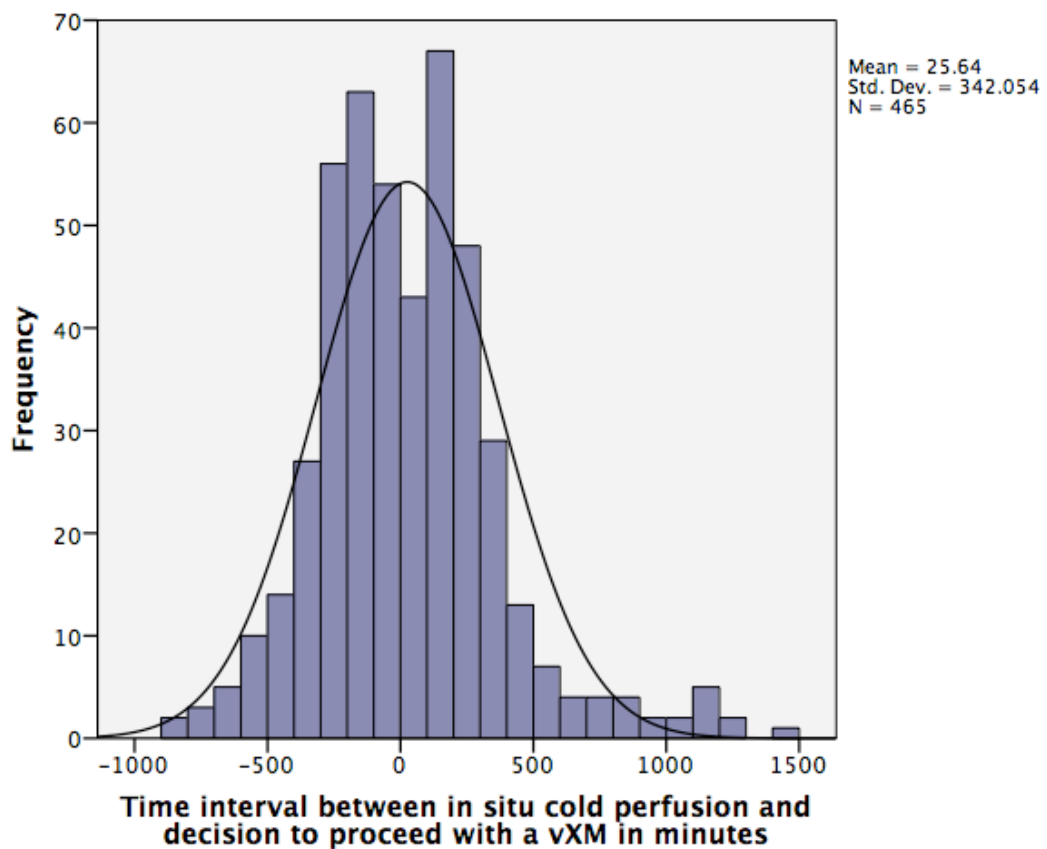


Significance:  $F=12.177$ ,  $p<0.0001$

### 3.7.1 Timing of decision to proceed to transplant with a vXM in relation to in situ cold perfusion

In majority of the cases, the decision to proceed with a vXM was made very early in the process of retrieval surgery as demonstrated by the fact that the timing of the decision was within a minute of start of CIT (in situ cold perfusion) (Figure 3.31).

**Figure 3.31 Distribution of time interval between in situ cold perfusion and decision to proceed to transplant with a vXM**



## 3.8 Pre-transplant crossmatch

### 3.8.1 Donor tissue used for pre-transplant crossmatching

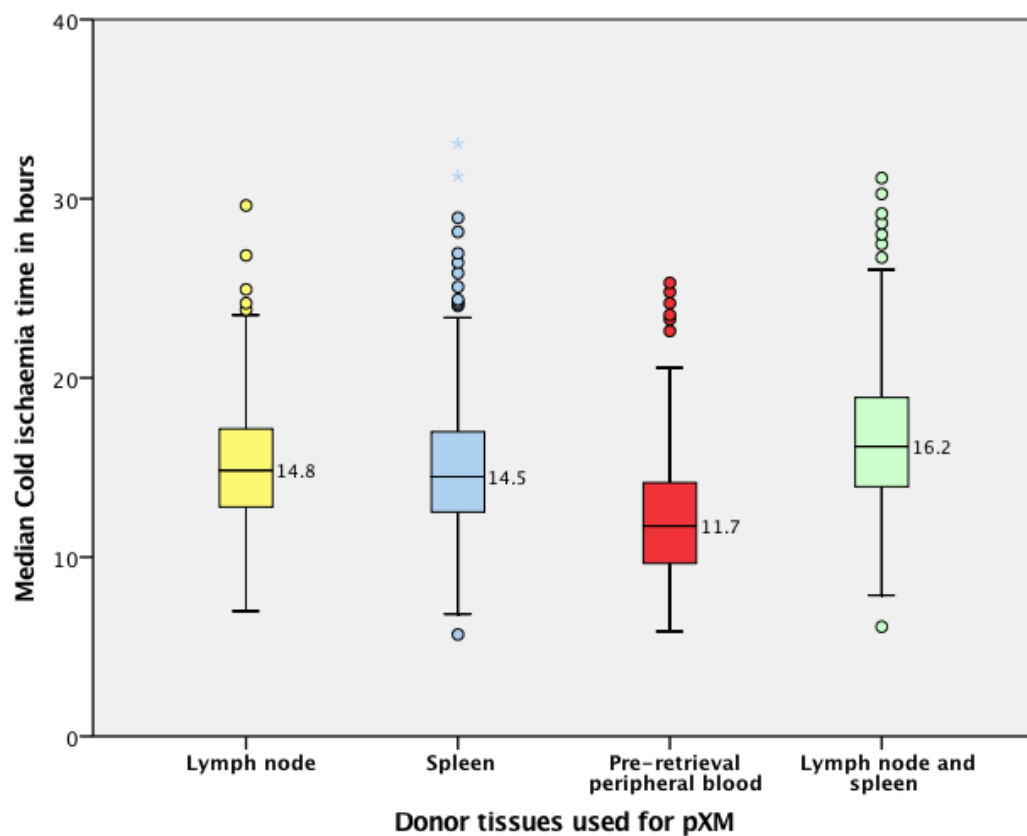
Pre-retrieval peripheral blood from donor for tissue typing is used to XM with recipient serum to establish HLA compatibility, and this is available for testing before the donor organs arrive at the recipient hospital. Other donor tissues that may be used are spleen and lymph nodes, which are transported with the donor organs. The donor tissue that was used the most for pXM was spleen (50.8%). (Table 3.17). Of the total pXM, 79% used donor tissue other than pre-retrieval peripheral blood.

**Table 3.17 Donor tissues for pXM**

<b>Donor Tissues for used for pXM</b>	<b>n (%)</b>
Pre-retrieval peripheral blood	224 (20.5)
Lymph node	94 (8.6)
Spleen	554 (50.8)
Lymph node and spleen	219 (20.1)

There was a significant difference in CIT between transplants that used donor pre-retrieval peripheral blood for pre-transplant crossmatching (pXM) and those that used other donor tissues. (Figure 3.32)

**Figure 3.32 Impact of type of donor tissue used for pXM on cold ischaemia time**



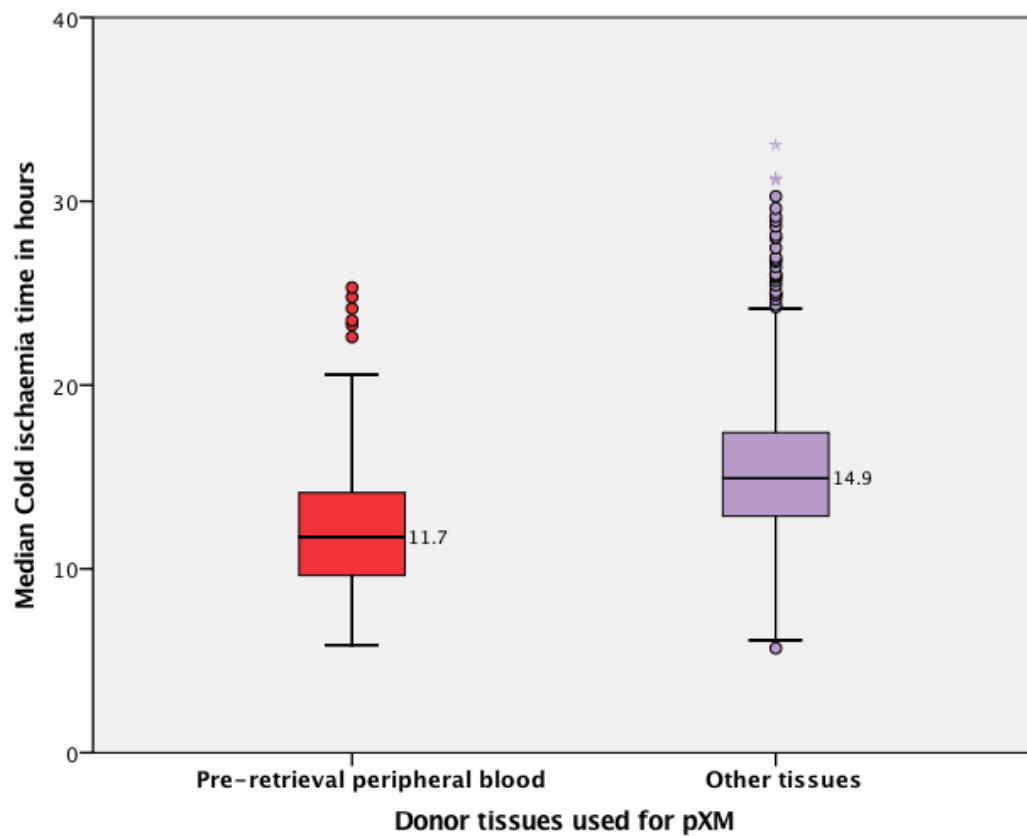
Significance:  $F= 54.710$ ,  $p<0.0001$

There was a significant difference in median CIT between transplants that used pre-retrieval peripheral blood and other donor tissue for pXM, with more than 3 hours' difference in CIT. (Table 3.18, Figure 3.33)

**Table 3.18 Cold ischaemia time for kidney transplants with pre-retrieval peripheral blood and other donor tissues for pXM**

Donor Tissue for pXM	CIT (Hours)	
	Mean (SD)	Median (IQR)
Pre-retrieval peripheral blood	12.2 (3.8)	11.7 (9.7-14.2)
Other donor tissues	15.5 (4.0)	14.9 (12.9-17.4)

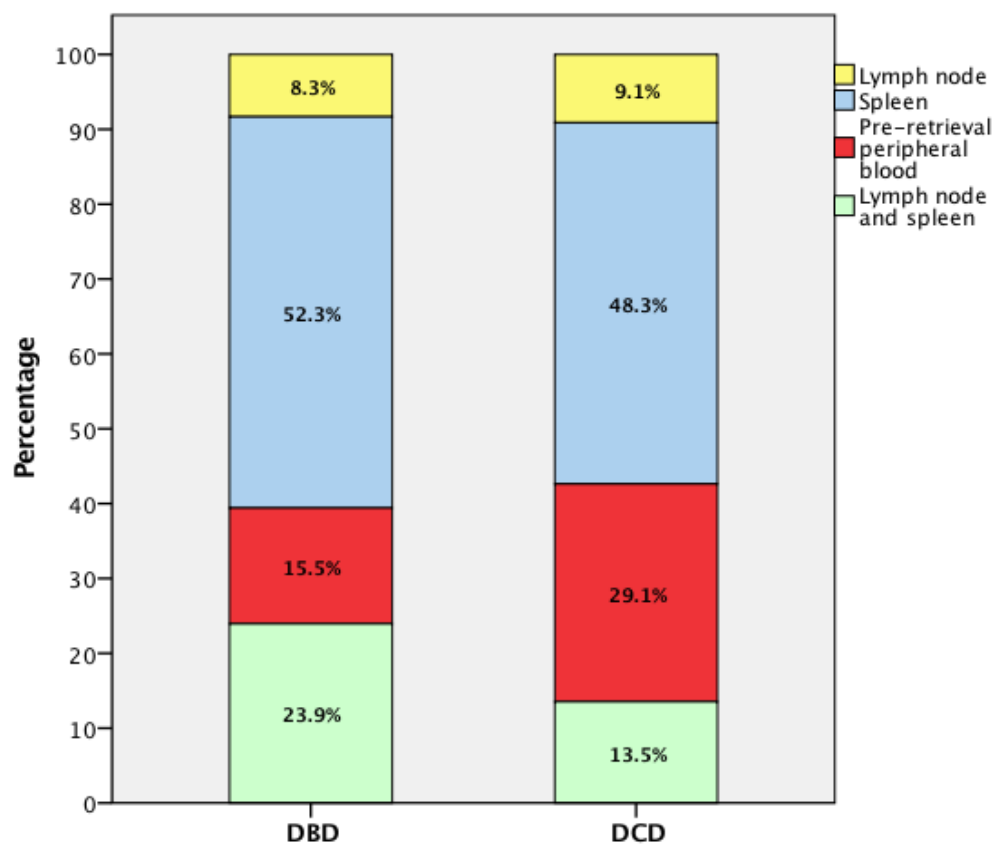
**Figure 3.33 Impact of pre-retrieval peripheral blood and other donor tissue used for pXM on cold ischaemia time**



Significance:  $F=137.978$ ,  $p<0.0001$

The majority of pXM used donor spleen in both DBD and DCD transplant (52% and 48, respectively). Twenty nine percent of pXM in DCD kidney transplant and 16% in DBD used donor pre-retrieval peripheral blood. (Figure 3.34)

**Figure 3.34 Donor tissues used for pXM in DBD and DCD kidney transplants**

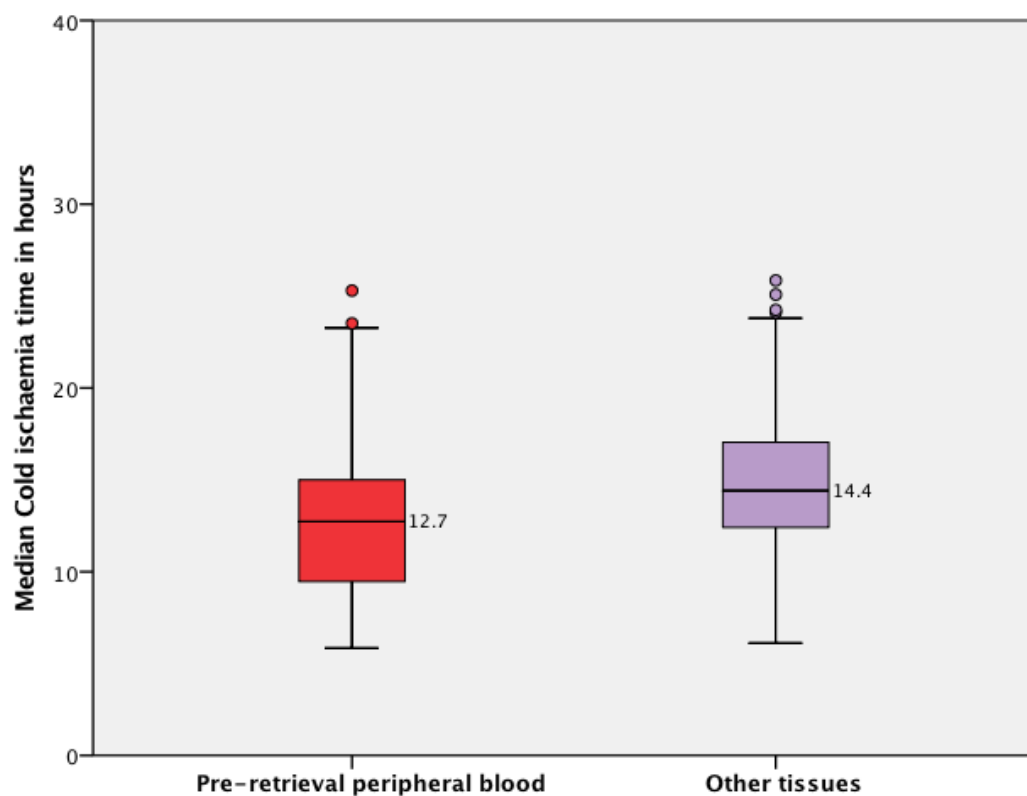




For DCD kidney transplants:

The median CIT for DCD kidney transplants that used pre-retrieval peripheral blood for pXM was 1.7 hours shorter than those that used other tissues (Figure 3.35).

**Figure 3.35 Impact of donor pre-retrieval peripheral blood versus other donor tissue used for pXM on cold ischaemia time in DCD kidney transplants**

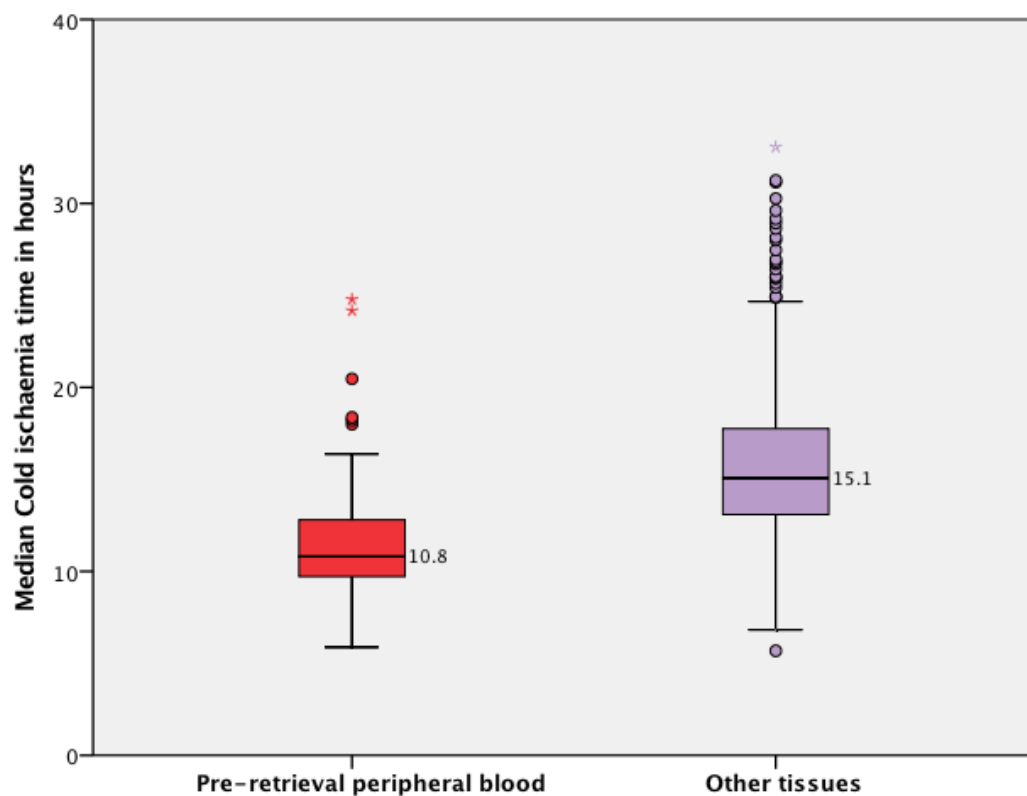


Significance:  $F=28.434$ ,  $p<0.0001$

For DBD kidney transplants:

There was more than 4 hours' difference in median CIT between those that used pre-retrieval peripheral blood and those that awaited lymph node and spleen for pXM within DBD transplants (10.8 hours and 15.1 hours, respectively), which is highly significant. (Figure 3.36)

**Figure 3.36 Impact of donor pre-retrieval peripheral blood versus other donor tissue used for pXM on cold ischaemia time in DBD kidney transplants**



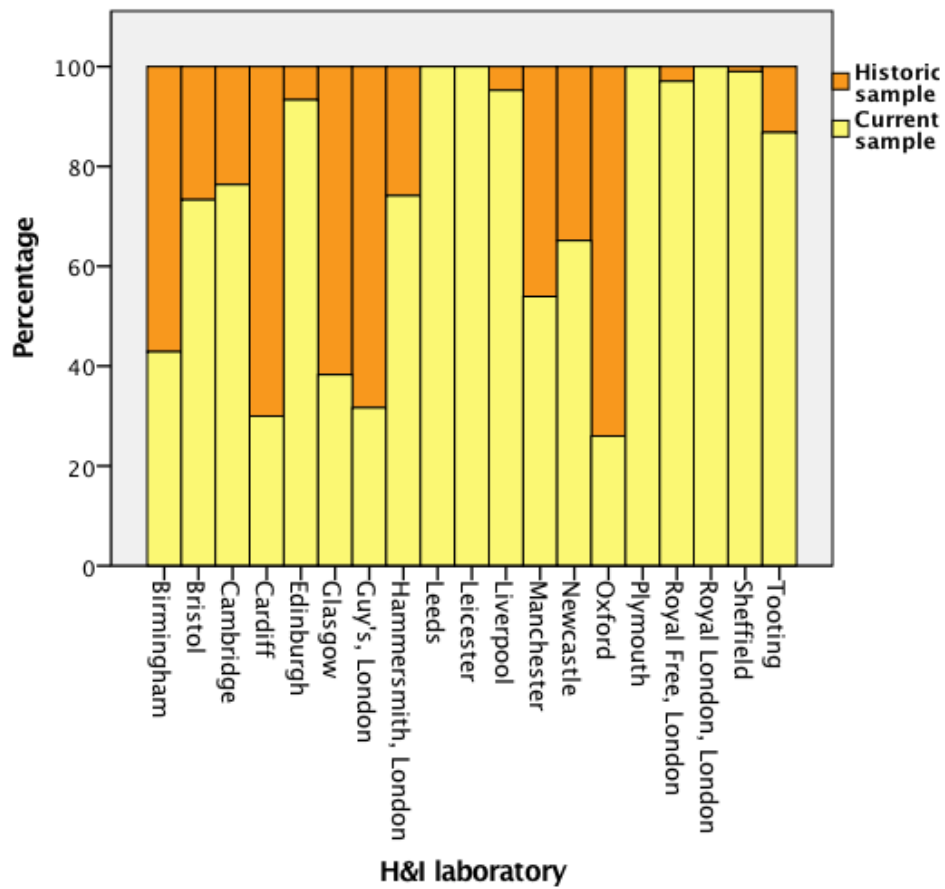
Significance:  $F=111.778$ ,  $p<0.0001$

### **3.8.2 Recipient serum sample used for prospective crossmatching**

Recipient serum samples used for pXM were either historic (stored sample) or current at the day of transplant ('at transplant' sample). 'At transplant' sample (current) was used for majority of the pXM (65%).

There was a wide H&I laboratory variation in the use of current and stored recipient sample for pXM. Four H&I laboratories used 'at transplant' recipient sample only. Three H&I laboratories used 'at transplant' recipient sample in less than 10% of their total transplants that required a pXM (Figure 3.37).

**Figure 3.37 H&I laboratory variation in the use of stored (historic) and ‘at transplant’ (current) recipient sample for pXM**

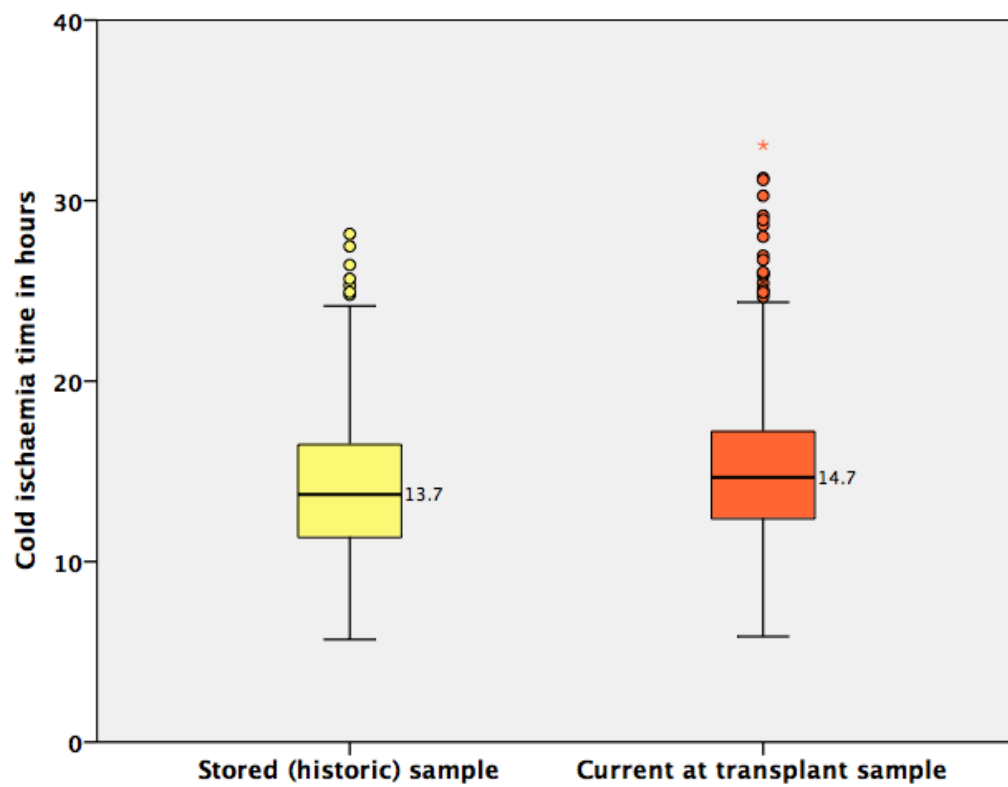


Transplants that used stored recipient serum sample for pXM had 1 hour shorter median CIT than those pXM that used ‘at transplant’ serum sample. (Table 3.19, Figure 3.38)

**Table 3.19 Cold ischaemia time for current at transplant or stored recipient serum sample used for pXM**

<b>Recipient serum sample</b>	<b>n</b>	<b>Mean (SD)</b>	<b>Median (IQR)</b>
Current (‘at transplant’)	710	15.1 (4.2)	14.7 (12.4-17.2)
Historic (stored)	390	14.0 (4.0)	13.7 (11.3-16.5)

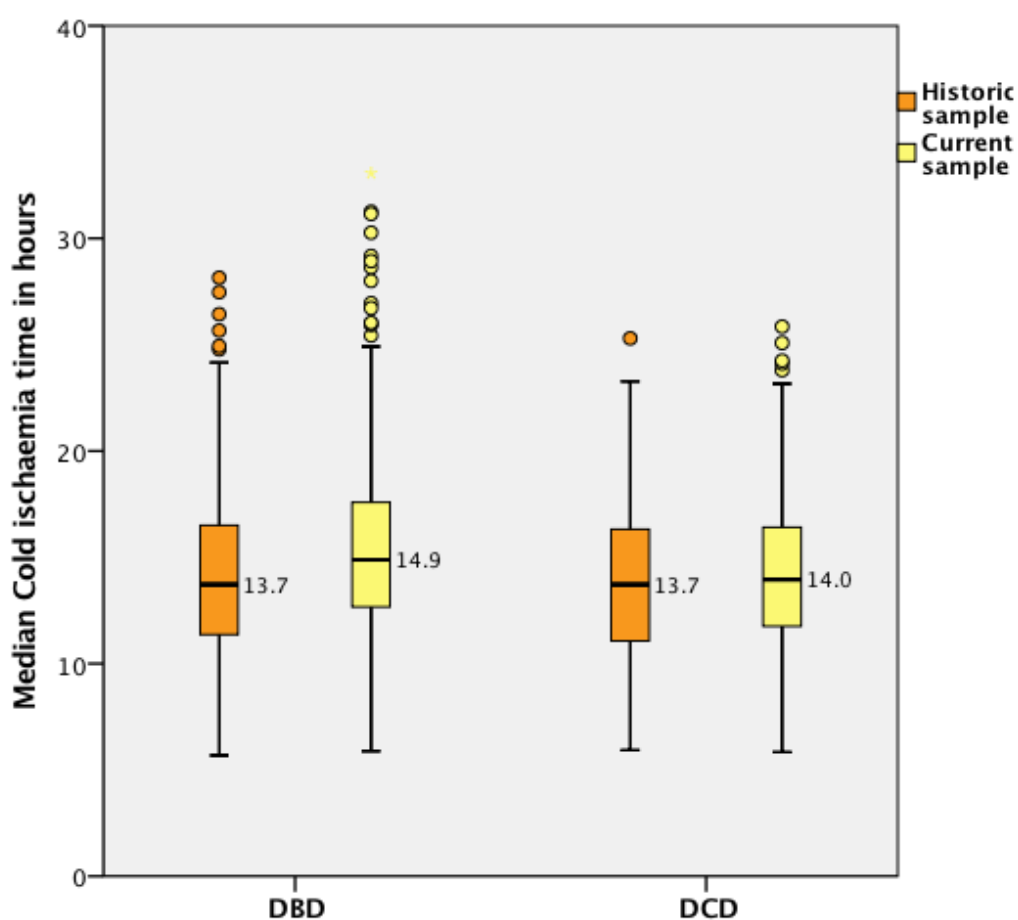
**Figure 3.38 Impact of historic (stored) and current ('at transplant') recipient serum sample for pXM on cold ischaemia time**



Significance:  $F=17.283$ ,  $p<0.0001$

The difference in median CIT between type of recipient sample used (current at transplant or stored) for pXM was significant for DBD transplants but not for DCDs. (Figure 3.39)

**Figure 3.39 Impact of historic and current recipient sample for pXM on cold ischaemia time in DBD and DCD kidney transplants**



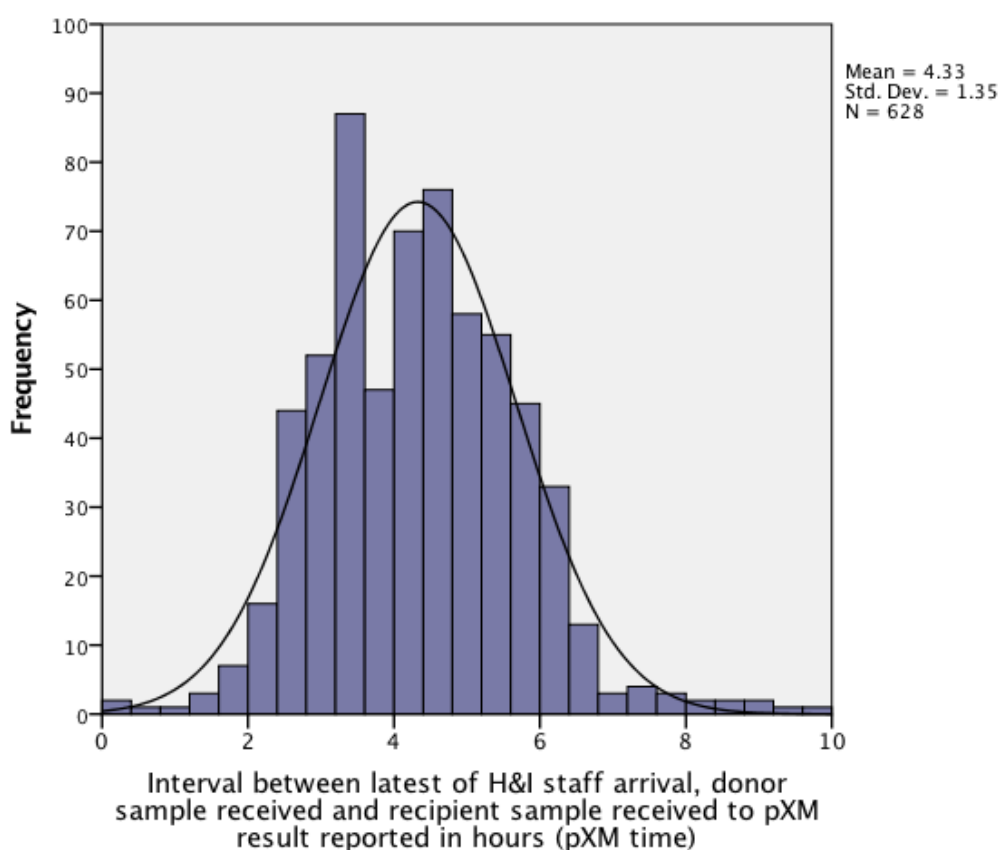
Significance: DBD:  $F=11.429$ ,  $p=0.001$

DCD:  $F=3.571$ ,  $p=0.60$

### 3.8.3 Timing of reporting of pre-transplant crossmatch result in relation to latest of H&I staff arrival, donor sample arrival and recipient sample collected

The median time for pXM result to be available after all facilities required to perform pXM are available, namely, arrival of H&I staff and delivery of donor sample to H&I laboratory and, obtaining recipient serum sample either historic or current (pXM time) was 4.3 hours (IQR 3.3-5.3). (Figure 3.40)

**Figure 3.40 Distribution of pXM time**

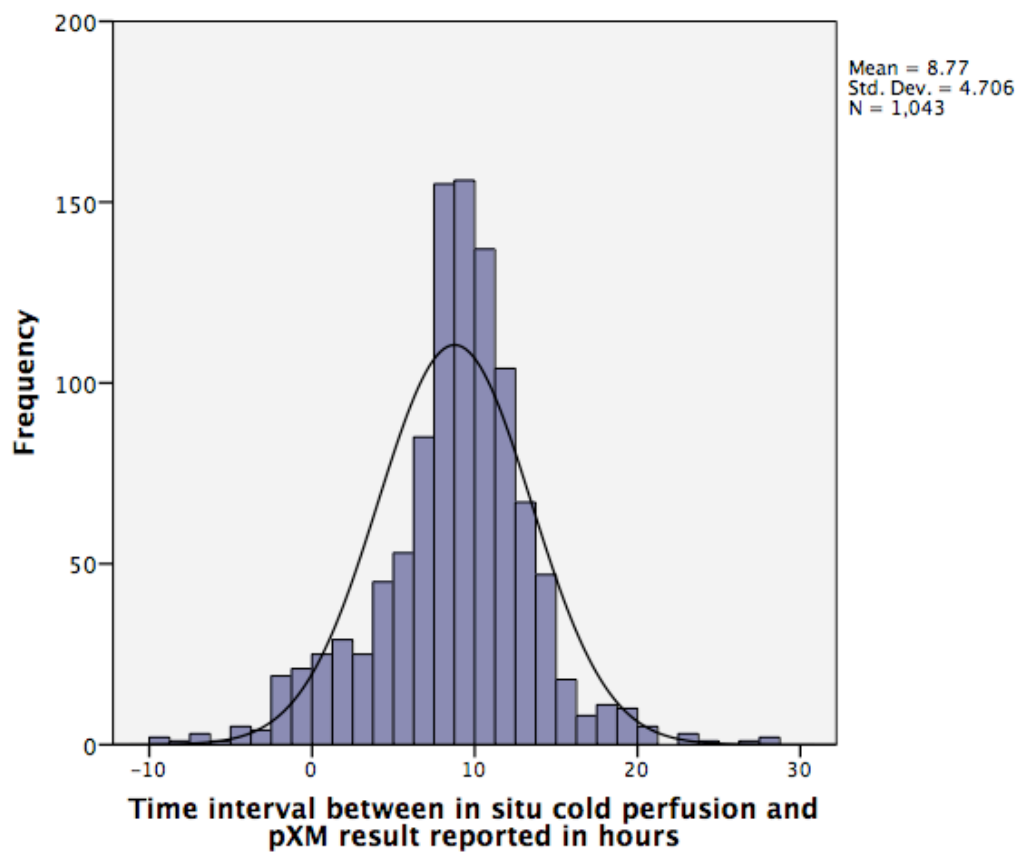




### 3.8.4 Timing of reporting of pre-transplant cross match result in relation to in situ cold perfusion

The median time interval between in situ cold perfusion (start of CIT) at retrieval surgery and pXM result report was 9.2 hours (IQR 6.7-11.4). (Figure 3.41)

**Figure 3.41 Distribution of time interval between in situ cold perfusion and reporting of pXM result**



### 3.9 Recipient preparation and impact on cold ischaemia time

#### 3.9.1 Recipient mode of travel to hospital for transplant

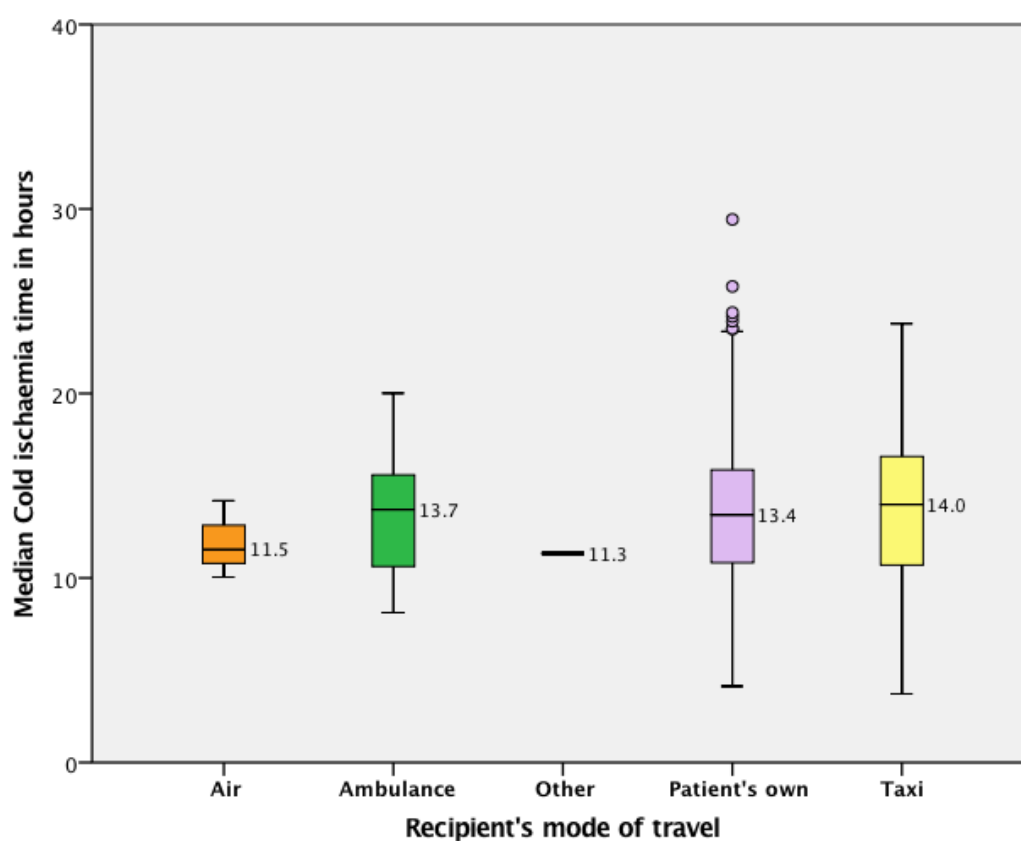
The data for recipient mode of transport to hospital for transplant were available for 619 transplants. The recipients used their own transport to travel to hospital in 79% of transplants. (Table 3.20)

**Table 3.20 Recipient mode of travel to hospital for transplant**

<b>Recipient mode of travel</b>	<b>n (%)</b>
Ambulance	33 (5.3)
Air	4 (0.6)
Patient's own	491 (79.3)
Taxi	90 (14.5)
Other	1 (0.2)

Recipient mode of transport to hospital for transplant did not impact CIT significantly. (Figure 3.42)

**Figure 3.42 Impact of recipient mode of travel on cold ischaemia time**



Significance:  $F=0.238$ ,  $p=0.917$

### 3.9.2 Requirement for haemodialysis immediately pre-transplant

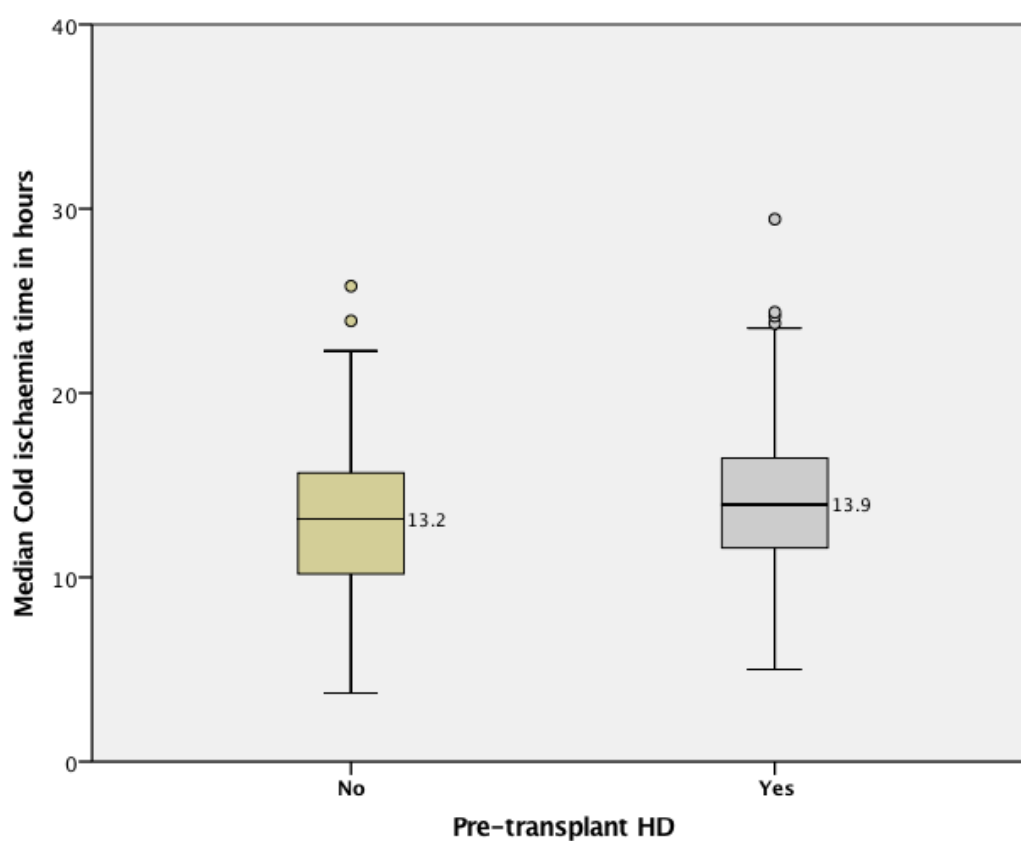
The data for whether or not haemodialysis (HD) was required for recipient immediately before proceeding to transplantation surgery were available for 664 transplants of which, almost a third required HD before transplant. The average duration for HD was 5 hours. The median CIT was almost an hour (54 minutes) longer when recipient required HD before transplantation. (Table 3.21)

**Table 3.21 Cold ischaemia time for transplants with or without recipient HD immediately before transplant**

Pre-transplant HD	CIT in hours	
	Mean (SD)	Median (IQR)
No	13.0 (3.9)	13.2 (10.1-15.7)
Yes	14.1 (4.2)	13.9 (11.6-16.5)

Whether or not recipient required HD immediately before transplantation had a significant impact on CIT. (Figure 3.43)

**Figure 3.43 Impact of recipient requirement for HD immediately pre-transplant on cold ischaemia time**



Significance:  $F=8.306$ ,  $p=0.004$

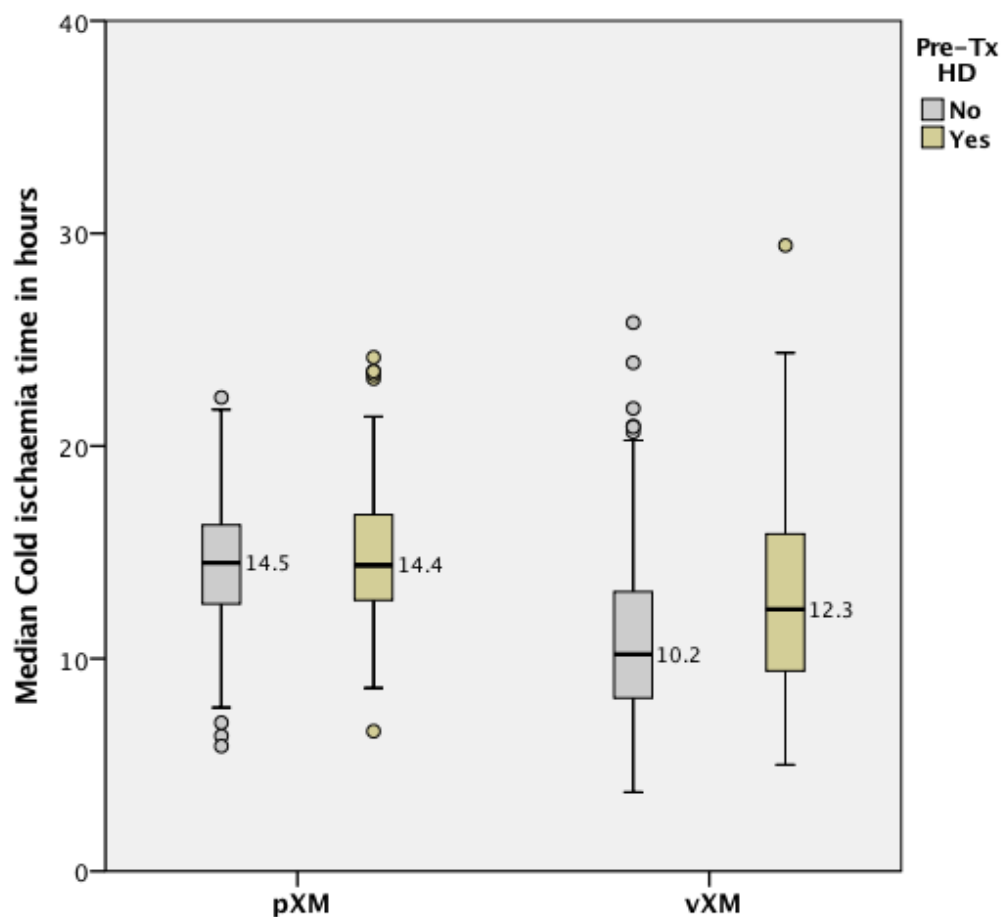
Median CIT was 2.1 hours longer for transplants with a vXM where recipient required HD before transplant. However, there was no difference in median CIT for transplants with pXM whether or not recipient required HD immediately before transplant. (Table 3.22)

**Table 3.22 Impact of recipient requirement for HD immediately pre-transplant with pXM and vXM on cold ischaemia time**

Pre-transplant HD	CIT in hours			
	pXM		vXM	
No	Mean (SD)	14.5 (3.1)	Mean (SD)	11.1 (4.1)
	Median (IQR)	14.5 (12.6-16.3)	Median (IQR)	10.2 (8.2-13.2)
Yes	Mean (SD)	15.0 (3.5)	Mean (SD)	13.1 (4.7)
	Median (IQR)	14.4 (12.7-16.8)	Median (IQR)	12.3 (9.4-15.9)

Whether or not recipient required HD before transplant impacted CIT significantly in vXM group, but did not impact on pXM group. (Figure 3.44)

**Figure 3.44 Impact of recipient requirement for HD immediately pre-transplant in pXM and vXM group on cold ischaemia time**



Significance: vXM group:  $F=11.758$ ,  $p=0.001$

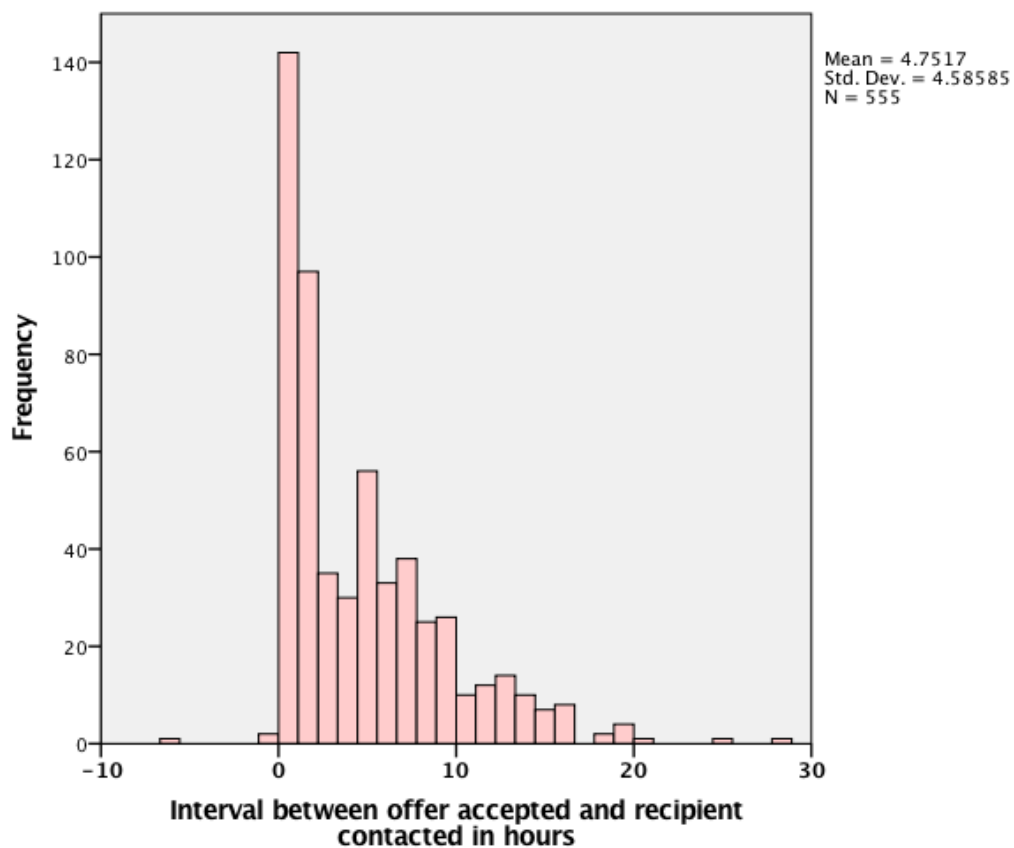
pXM group:  $F=1.699$ ,  $p=0.193$

In the pXM group, there was no significant impact of recipient requirement for dialysis immediately pre-transplant in XM with donor pre-retrieval peripheral blood and XM with other donor tissues group on CIT.

### 3.9.3 Timing of contact of recipient for kidney transplantation after kidney offer accepted

The data were available for 555 transplants. Three recipients were contacted before offer was officially accepted. One of the recipients was contacted 6 hours before, for DCD donor transplantation at the same hospital. The other two recipients were contacted 24 minutes and 25 minutes before, respectively. The median time interval between accepting kidney offer and contacting recipient for transplantation was 3.3 hours (IQR1.1-1.72). (Figure 3.45)

**Figure 3.45 Distribution of time interval between offer accepted and recipient contacted for kidney transplantation**

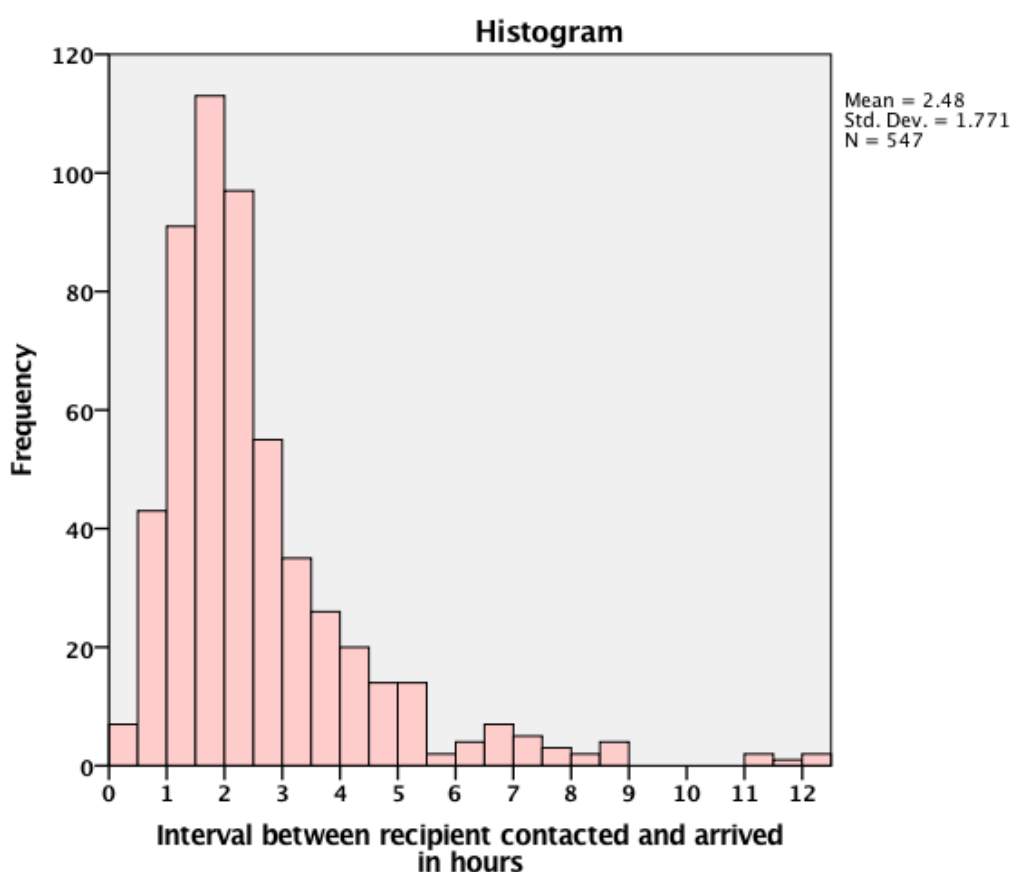




### 3.9.4 Timing of arrival of recipient in hospital for transplantation after recipient contacted

The data were available for 547 transplants. The majority of the patients arrived within 2 hours of being contacted for transplantation (median 2.0 hours, IQR 1.4-3.0). One of the recipients was already in hospital receiving dialysis at the time of contact. (Figure 3.46)

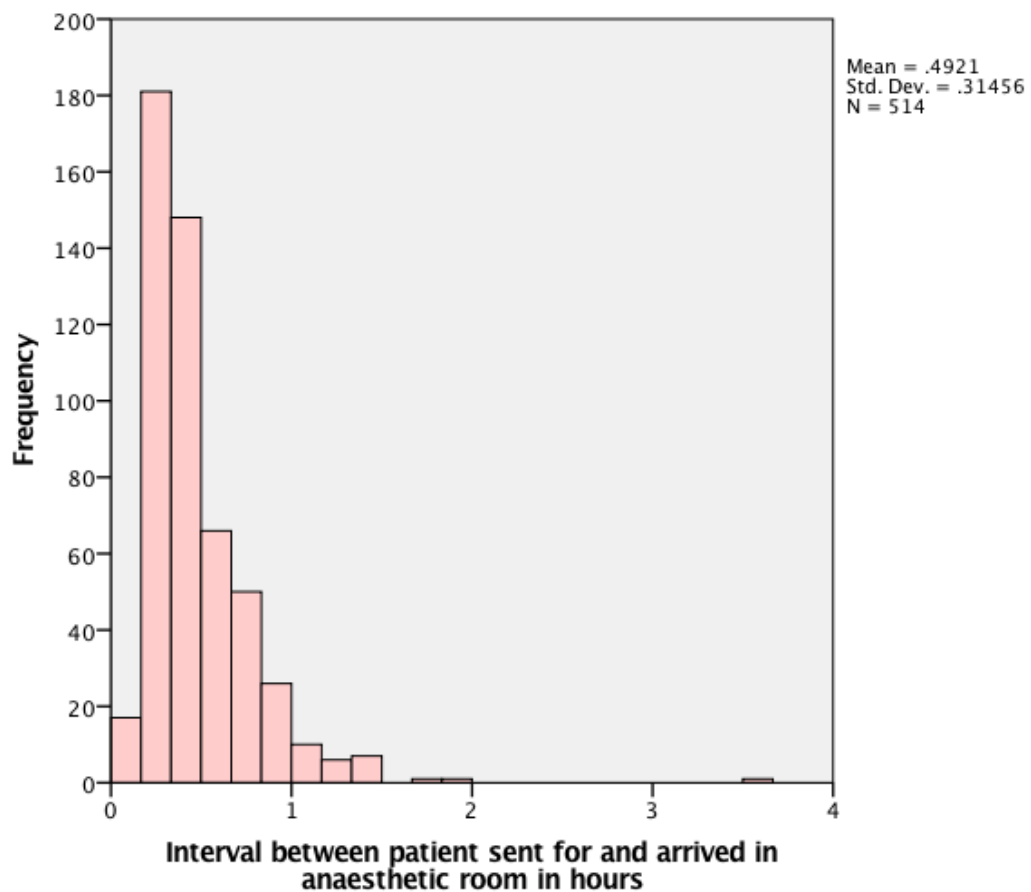
**Figure 3.46 Distribution of time interval between recipient contacted and arrived for transplant**



### 3.9.5 Timing of arrival of recipient in anaesthetic room after porter sent to bring recipient to theatre

Data were available for 514 patients. The median time for arrival of recipient in anaesthetic room after being sent for was 25 minutes (median 0.42 hours, IQR 0.28-0.60). (Figure 3.47)

**Figure 3.47 Distribution of time interval between recipient sent for and arrived in anaesthetic room**



### **3.10 Theatre factors and impact on cold ischaemia time**

#### **3.10.1 Access to theatre**

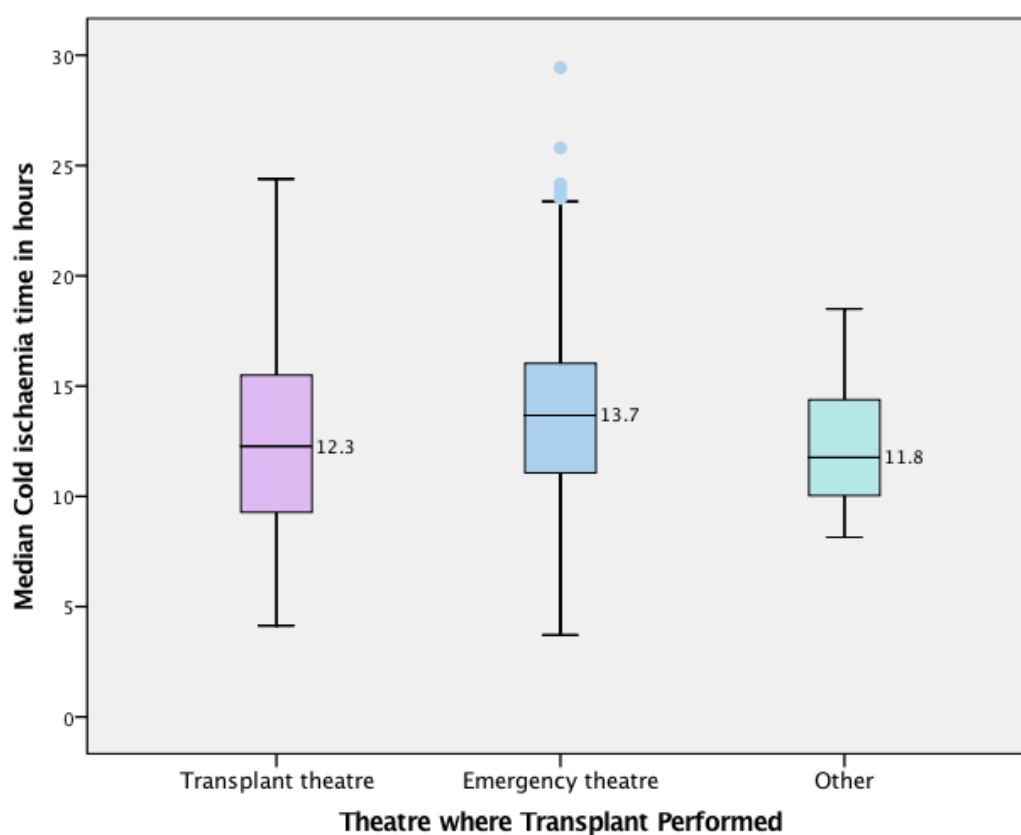
Majority of transplants were performed in emergency theatre (76%). Only 22% kidney transplants had access to dedicated transplant theatre.

Median CIT for kidneys transplanted in dedicated transplant theatre was 1.4 hours shorter than for those transplanted in either emergency or other theatres, where elective procedures are carried out. Typically, access to a dedicated transplant theatre for kidney transplantation had a significant impact on CIT. (Table 3.23, Figure 3.48)

**Table 3.23 Cold ischaemia time in relation to access to theatre**

Theatre	n (%)	CIT in hours				
		Mean	SD	Minimum	Maximum	Median (IQ Range)
Transplant Theatre	148 (22.2)	12.6	4.0	4.1	24.4	12.3 (9.3-15.5)
Emergency Theatre	508 (76.3)	13.6	4.0	3.7	29.4	13.7 (11.1-16.0)
Other	10 (1.5)	12.3	3.1	8.2	18.5	11.8 (9.8-14.5)

**Figure 3.48 Impact of theatre access on cold ischaemia time**

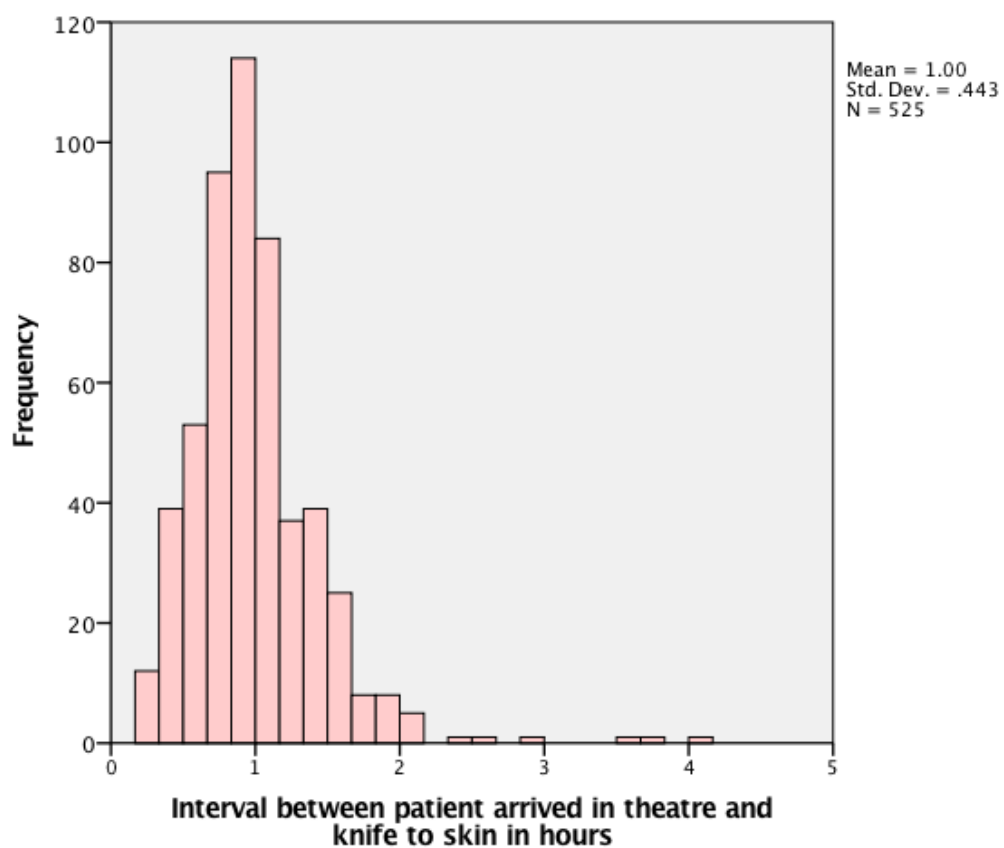


Significance: F-3.393, p=0.034

### 3.10.2 Timing of start of transplant surgery (knife to skin) in relation to arrival of recipient in anaesthetic room

The data were available for 525 transplants. It took an hour on average to prepare and anaesthetise recipient in the anaesthetic room before surgery (median 1.0 hours, IQR 0.75-1.2). (Figure 3.49)

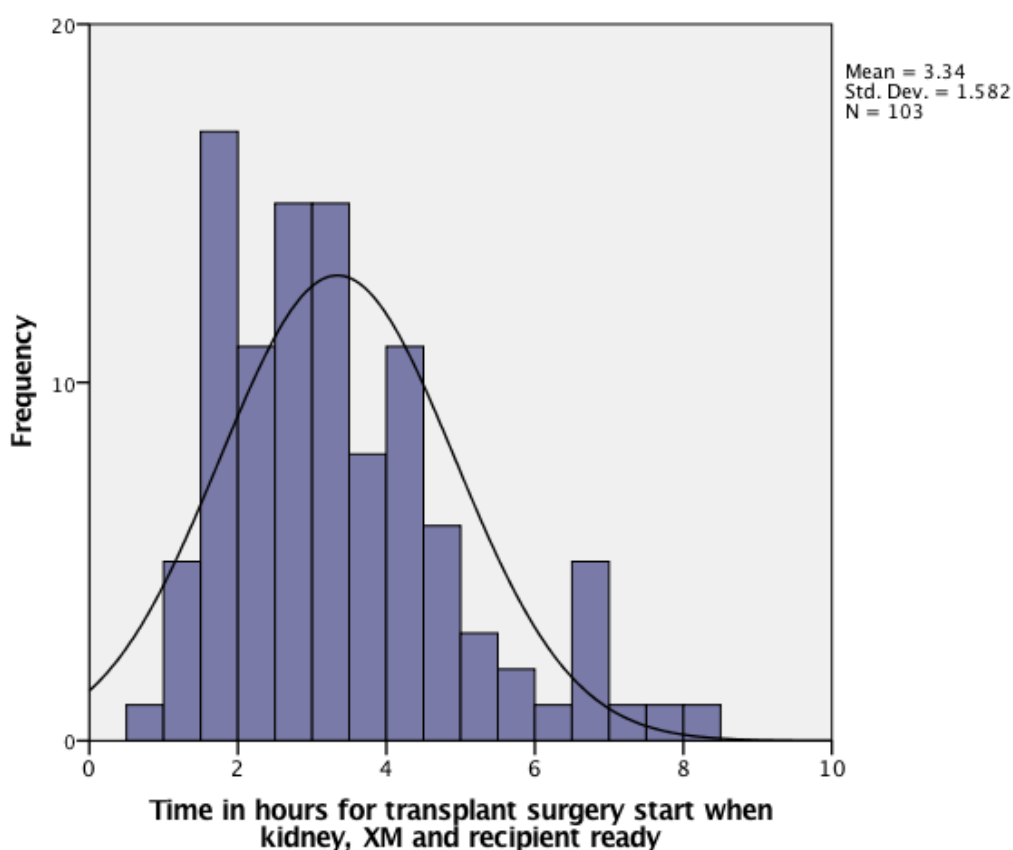
**Figure 3.49 Distribution of recipient time in anaesthetic room**



### 3.10.3 Timing of start of transplant surgery (knife to skin) in relation to completion of crossmatching, recipient preparation and kidney delivery

The data were available for 103 transplants. When recipient preparation was complete including HD where required, pXM was complete and result reported and kidneys were delivered at the transplanting hospital, there was still a delay of a median of 3 hours (IQR 2.1-4.2) for transplant surgery start. (Figure 3.50)

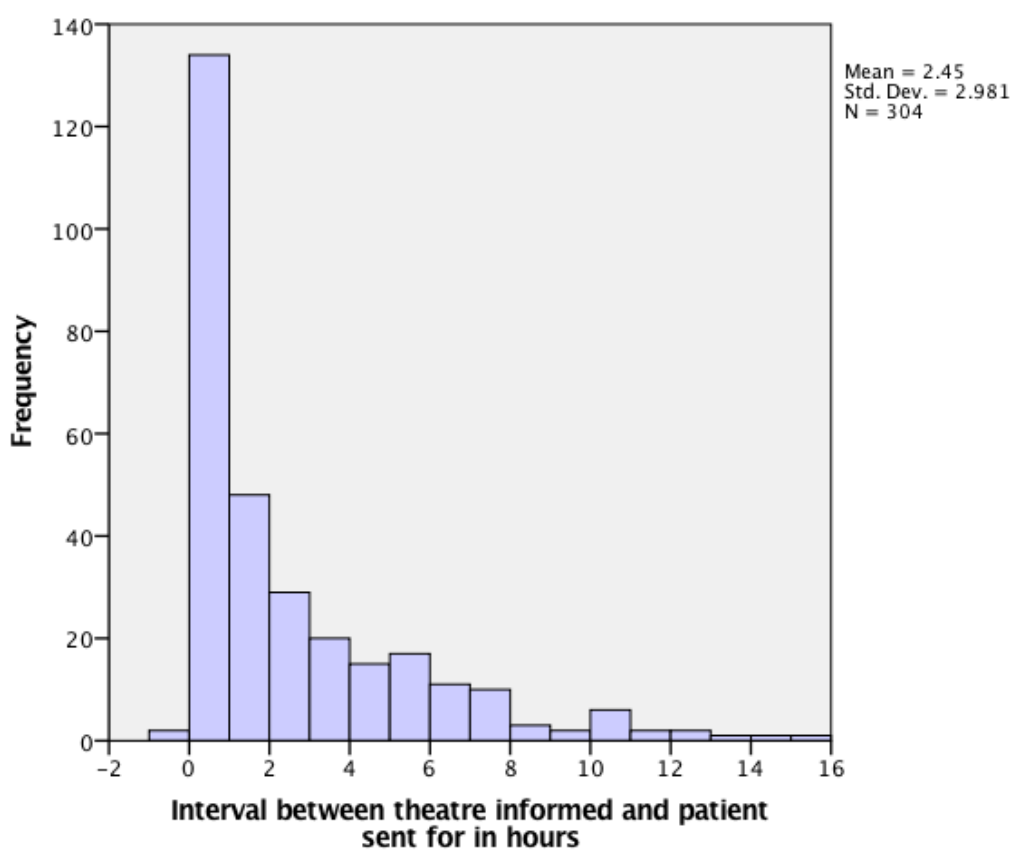
**Figure 3.50 Distribution of time interval between completion of all preparation for transplant and knife to skin**



### 3.10.4 Time interval between informing theatre and sending for recipient for transplant

Data were available for 304 transplants. Median time between informing theatre and sending for the recipient to start surgery was 1.1 hours (IQR 0.34-3.42). Some of the intervals were longer because theatres were informed soon after offers were accepted rather than waiting until all preparations were completed. (Figure 3.51)

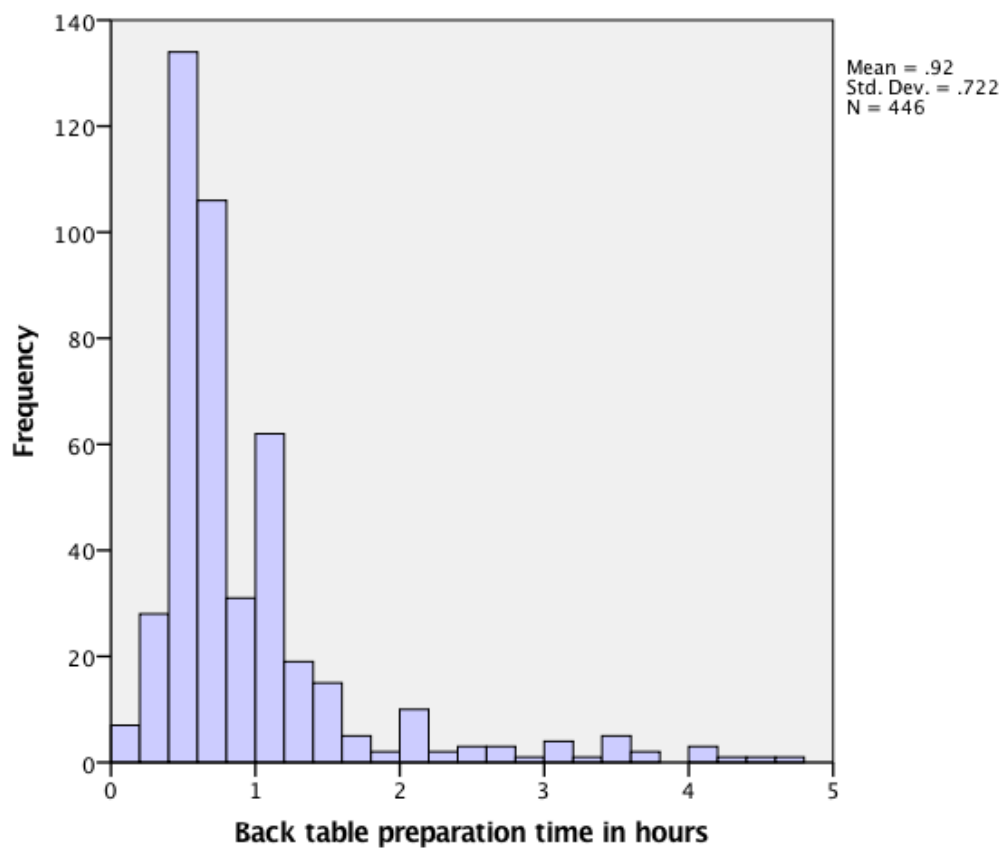
**Figure 3.51 Distribution of time interval between informing theatre and sending for recipient for surgery**



### 3.10.5 Back table preparation time for donor kidney

The data were available for 446 transplants. An average of 54 minutes was required for preparation of donor kidney before transplanting into recipient. (Figure 3.52)

**Figure 3.52 Distribution of back table preparation time**

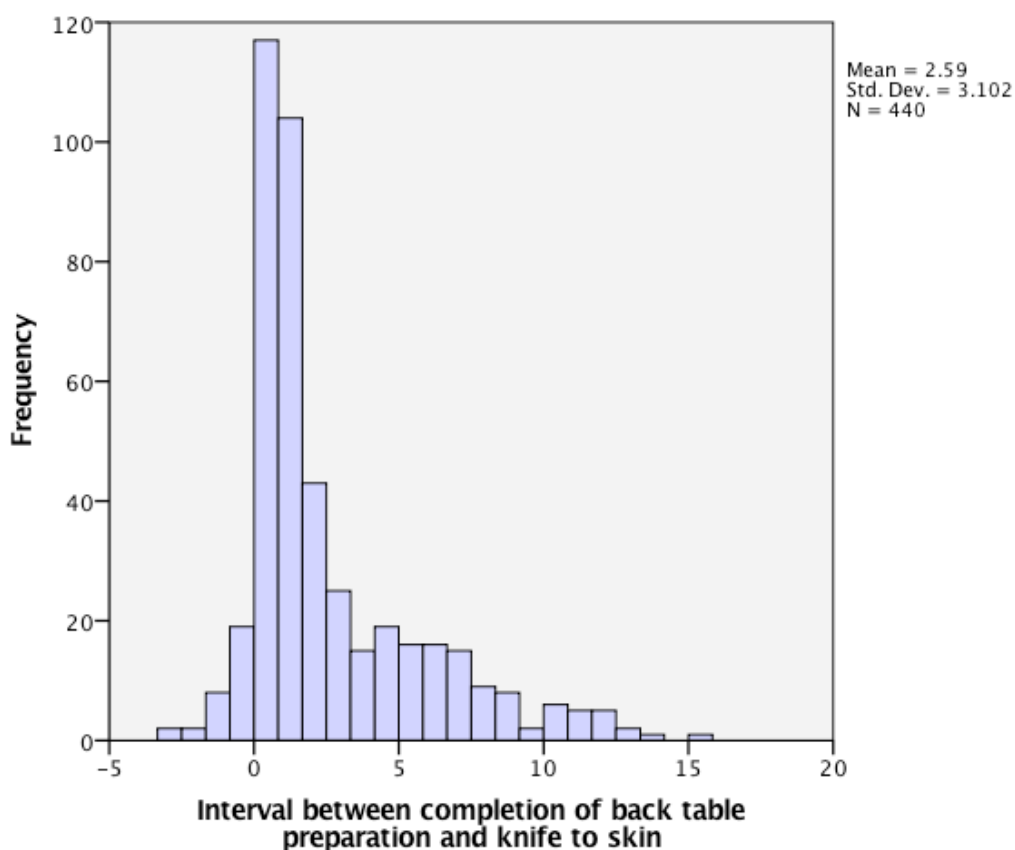




### 3.10.6 Timing of knife to skin after back table preparation of donor kidney

The data were available for 440 transplants. Median time between completion of back table preparation and start of transplant surgery was 1.3 hours (IQR 0.6-3.9). The majority of transplants where transplant surgery started before completion of back table preparation was SPK transplants (19 out of 30). (Figure 3.53)

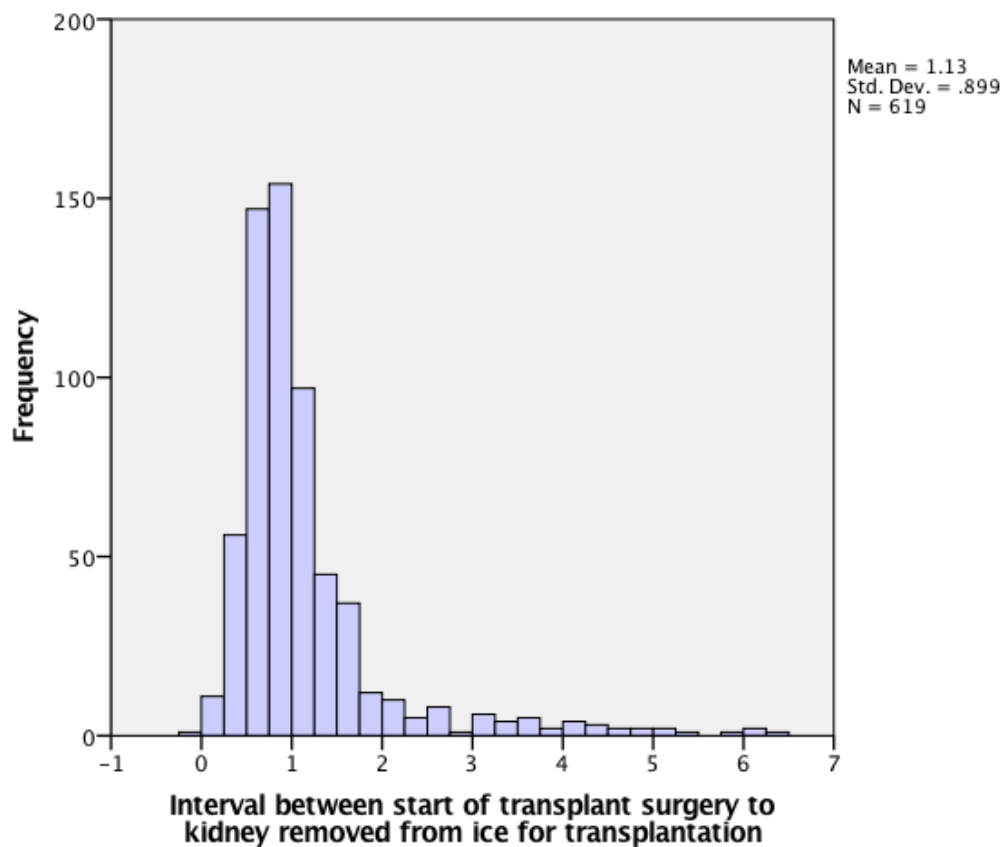
**Figure 3.53 Distribution of time interval between completion of back table preparation and knife to skin**



### 3.10.7 Timing of removal of donor kidney from ice for anastomosis in recipient in relation to start of transplant surgery

The data were available for 619 transplants. Median time between knife to skin at transplant surgery and donor kidney removed from ice for anastomosis into recipient was less than an hour (median 0.9 hours, IQR 0.7-1.2). (Figure 3.54)

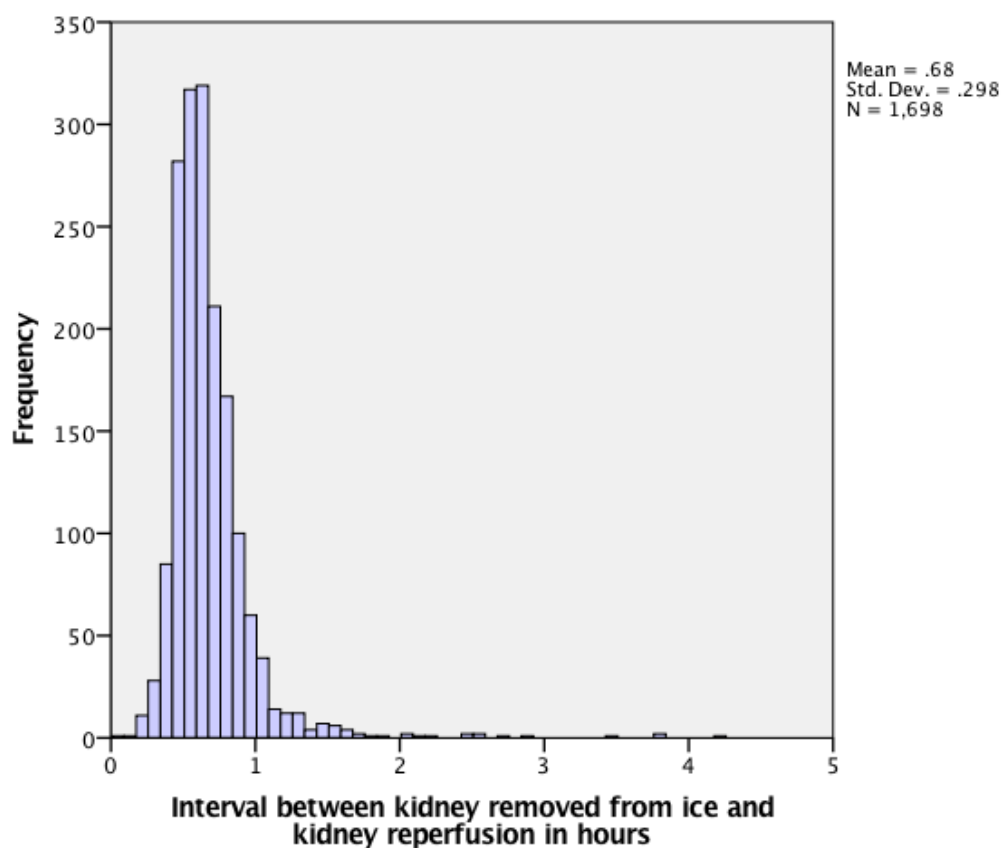
**Figure 3.54 Distribution of time interval between knife to skin and donor kidney removal from ice for anastomosis into recipient**



### 3.10.8 Timing of reperfusion of kidney after removal of donor kidney from ice at transplantation surgery

The data were available for 1698 transplants. Median time between removal of donor kidney from ice for transplantation into recipient at transplant surgery and re-establishment of circulation and perfusion of the kidney in the recipient was 36 minutes (IQR 0.1-0.8). (Figure 3.55)

**Figure 3.55 Distribution of time interval between removal of donor kidney from ice and re-establishment of kidney perfusion**

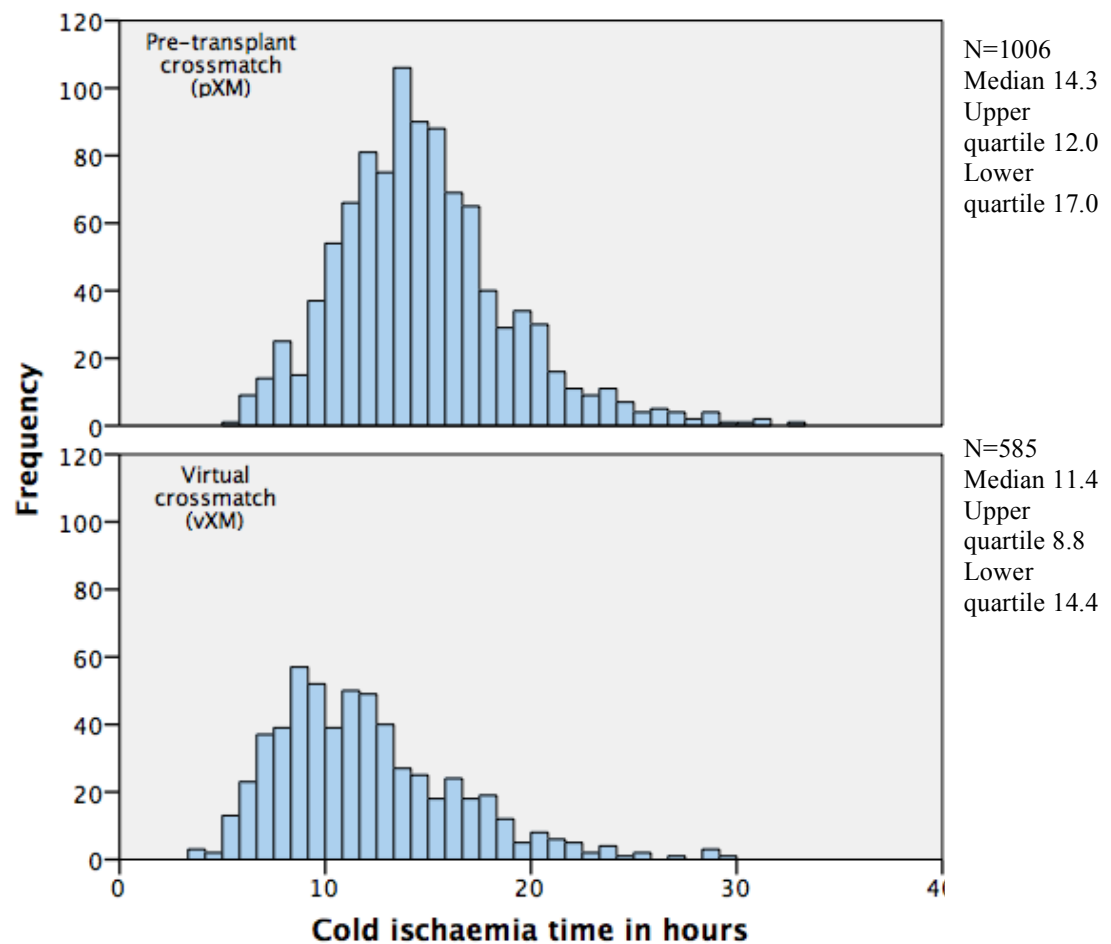


### **3.11 Univariate and multivariate analysis of significant factors contributing to cold ischaemic time**

Cold ischaemia time was significantly shorter ( $p < 0.0001$ ) when deceased donor kidney transplants were performed with a virtual crossmatch (vXM) as compared to those that were performed after prospective pre-transplant crossmatch (pXM). Therefore, two separate models were investigated for vXM and pXM to determine the factors that significantly contributed to the overall cold ischaemia time (CIT).

Figure 3.56 shows the distribution of CIT for both pXM and vXM. The median CIT for pXM ( $n=1006$ ) is 14.3 hours (IQR 12.0 – 17.0). The median CIT for vXM ( $n=585$ ) is 11.4 hours (IQR 11.4 – 14.4).

**Figure 3.56 Distribution of cold ischaemia time in kidney transplants with pXM and vXM**



Significance:  $F=77.086$ ,  $p<0.0001$

### 3.11.1 Prospective pre-transplant crossmatch

Univariate analysis of categorical and continuous factors contributing to cold ischaemia time in transplants with pXM was performed. (Tables 3.24, 3.25)

**Table 3.24 Univariate analysis for categorical factors contributing to cold ischaemia time in minutes**

Factor	Level	N	%	p-value
Donor type	DBD	703	62	0.0003
	DCD	424	38	
Local	No	740	66	<0.0001
	Yes	387	34	
Reallocated kidney	No	1104	98	0.0007
	Yes	23	2	
Peripheral blood	No	867	79	<0.0001
	Yes	224	21	
	Missing	36	-	
Current sample	No	389	35	<0.0001
	Yes	709	65	
	Missing	29	-	
Patient travel	1 (Ambulance)	20	6	0.5
	3 (Patient's own)	286	81	
	4 (Taxi)	46	13	
	5 (Other)	1	<1	
	Missing	774	-	
Haemodialysis required	No	261	71	0.2
	Yes	106	29	
	Missing	760	-	

**Table 3.25 Univariate analysis for continuous factors contributing to cold ischaemia time in minutes**

<b>Factor</b>	<b>N</b>	<b>Median</b>	<b>IQ Range</b>	<b>p-value</b>
Cold perfusion to kidney in ice box	867	76	61 - 93	0.04
Offer accepted to latest (staff in lab, donor sample arrive, recipient sample arrive)	308	565	372 - 780	0.006
Offer accepted to recipient contacted	292	108	28 – 395	0.01
Recipient contacted to recipient arrived	307	120	80 – 180	0.18
Kidney collected to kidney delivered	426	110	65 – 190	<0.0001
Kidney on ice to kidney collected	405	56	40 – 75	0.0004
Matching run complete to pXM result	1100	865	631 – 1141	<0.0001
Latest (xm result known, organ delivered, patient ready) to transplant surgery started	345	64	48 – 95	0.4
Transplant surgery started to kidney out of ice	354	54	39 - 75	0.77

The continuous factors that were significant on their own were categorised to include a missing category. Multivariate analysis included following factors in the pXM group that remained significant.

**Table 3.26 Multivariate analysis for factors contributing to cold ischaemia time**

<b>Factor</b>	<b>Level</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>p-value</b>
Intercept		864.13	18.8	<0.0001
Peripheral blood	No	Baseline		
	Yes	-193.7	18.9	<0.0001
Kidney collected to kidney delivered	Less than 2hrs	Baseline		
	2 – 4hrs	93.97	27.61	0.0007
	More than 4hrs	138.83	36.58	0.0002
	Missing	89.10	19.70	<0.0001
Kidney reallocated	No	Baseline		
	Yes	153.43	51.68	0.0031
Cold perfusion to Kidney on ice	Less than 1hr30	Baseline		
	More than 1hr30	63.01	18.60	0.0007
	Missing	47.72	18.72	0.01

In summary, for pXM group:

1. Median CIT for transplants that required pXM was 14.3 hours.
2. CIT was 3.2 hours shorter when donor pre-retrieval peripheral blood was used for pXM.
3. CIT was significantly longer when kidney transport time was above 2 hours.
4. CIT was 2.9 hours longer when kidney was reallocated.
5. CIT was significantly longer when time between in situ cold perfusion and kidney put in ice-box is more than 1.5 hours.



### 3.11.2 Virtual crossmatch

Univariate analysis of categorical and continuous factors contributing to cold ischaemia time in transplants with vXM was performed.

**Table 3.27 Univariate analysis for categorical factors contributing to cold ischaemia time in minutes**

Factor	Level	N	%	p-value
Donor type	DBD	333	52	0.01
	DCD	303	48	
Local	No	390	61	0.04
	Yes	246	39	
Reallocated kidney	No	616	97	<0.0001
	Yes	20	3	
Patient travel	1 (Ambulance)	13	5	0.9
	2 (Air)	4	2	
	3 (Patient's own)	205	77	
	4 (Taxi)	44	17	
	Missing	370	-	
Haemodialysis required	No	186	67	0.003
	Yes	91	33	
	Missing	359		

**Table 3.28 Univariate analysis for continuous factors contributing to cold ischaemia time in minutes**

<b>Factor</b>	<b>N</b>	<b>Median</b>	<b>IQ Range</b>	<b>p-value</b>
Cold perfusion to kidney in ice box	475	77	61 – 97	0.009
Offer accepted to agreement to proceed with a vXM	197	180	68 – 380	0.59
Offer accepted to recipient contacted	222	158	39 – 375	<0.0001
Recipient contacted to recipient arrived	240	120	90 – 180	0.54
Kidney collected to kidney delivered	221	130	80 – 205	0.0002
Kidney on ice to kidney collected	201	60	40 – 85	0.0005
Matching run complete to vXM result	494	266	96 – 550	<0.0001
Latest (xm result known, organ delivered, patient ready) to transplant surgery started	255	58	45 – 75	0.1
Transplant surgery started to kidney out of ice	264	52	42 - 73	0.03

Multivariate analysis included following factors in the vXM group that remained significant.

**Table 3.29 Multivariate analysis of factors contributing to cold ischaemia time**

<b>Factor</b>	<b>Level</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>p-value</b>
Intercept		580.00	31.82	<0.0001
Donor type	DCD	Baseline		
	DBD	47.48	21.98	0.03
Recipient on HD	No	Baseline		
	Yes	102.22	33.31	0.002
	Missing	76.09	24.07	0.002
Kidney reallocated	No	Baseline		
	Yes	338.45	60.12	<0.0001
Kidney collected to Kidney delivered	Less than 2hrs	Baseline		
	2 – 4hrs	97.47	38.72	0.01
	More than 4hrs	159.48	53.99	0.003
	Missing	99.26	29.00	0.0007

In summary, for vXM group:

1. Median CIT for transplants with a vXM was 11.4 hours.
2. CIT was 47 minutes longer for DBD donors than for DCD donors
3. CIT was 2.1 hours longer when recipient required HD immediately before transplant.
4. CIT was 5.3 hours longer when kidney was reallocated.
5. CIT was significantly longer when kidney transport time was more than 2 hours.

## 4 Discussion

A period of cold ischaemia is inevitable in the context of national allocation policy for deceased donor kidney transplantation in the UK to ensure equity of access and best immunological match for patients on the waiting list for transplantation.

Because of the discrepancy in wait-listed patients requiring kidney transplantation with the available kidneys, there is little choice but to adopt alternative strategies such as accepting kidneys from extended criteria donors (ECD) to meet the demand.

For a successful outcome, the length of time of cold storage is of crucial importance as it is recognised to be a significant risk factor for poorer outcomes including DGF, AR and short and long-term graft survival. Cold ischaemia time is also one of the few potentially modifiable risk factors in deceased donor kidney transplantation. In the current climate of continuing rise of use of ECD kidneys, CIT remains relevant and hence, there is an overarching need to minimise it. This is clearly demonstrated by the activities of Eurotransplant Senior Programme (Bahde et al., 2014).

The study illustrates the multifactorial and complex nature of the logistical factors that impact CIT in relation to the national allocation scheme for DBD and regional allocation policy for DCD kidney transplants in the UK. The logistics of organ retrieval, matching, transport and transplantation are not uniform between transplant centres, countries and networks for organ sharing but the challenges are similar. Despite the obvious need for investigation, there is a dearth of studies in the current literature that examines the process comprehensively. A regional case-controlled

French study managed to reduce CIT from 21 hours to 13 hours in nationally and locally allocated kidneys simply by introducing a timesheet on CIT (Vacher-Coponat et al., 2007). This also resulted in a significant reduction in the incidence of DGF. Another study from Chile identified several factors relating to organ sharing, HLA typing and crossmatching that impacted on CIT (Elgueta et al., 2010).

The single most important factor that contributed to CIT in this study was the introduction of a vXM policy. The Cambridge team pioneered the introduction of the vXM policy in the UK almost two decades ago. They have shown that selective omission of pre-transplant crossmatch is the most effective way to reduce CIT and that vXM policy can be safely introduced in carefully selected patients (Taylor et al., 2000, Taylor et al., 2010). Decision to proceed with a vXM is a paper exercise and it can be achieved soon after kidney is offered for transplant, often before retrieval surgery. In 61% of the transplants, the decision was made before kidney was put on ice and 39% within a median of 2.8 hours after. Remarkably, there was only a minute's delay on average for the decision to proceed with a vXM from the time of in situ cold perfusion at donor surgery suggesting that, effectively, vXM had zero impact on CIT. Despite early decision, kidney transplant surgery commenced 10 hours (median) after vXM decision suggesting delays with transport of kidneys, recipient preparation and theatre availability. Although the role of vXM policy is compelling, a single centre Swiss study did not show a significant influence of vXM on CIT. It demonstrated that vXM policy influenced expeditious allocation of kidneys to compatible recipients, enhanced risk stratification for modified

immunosuppressive therapy and reduced demand on H&I staff but did not influence CIT significantly (Amico et al., 2011).

The evidence could be used to inform national and international transplant communities as the purpose for adopting a vXM policy is not uniform. In the United States it is used solely as a tool to evaluate if a kidney is suitable to be shipped to a distant transplant centre for transplantation into sensitised patients. A negative pXM result is still a pre-requisite for a transplant to proceed. In this context, there is clear scope to reduce CIT by reviewing and safely implementing a vXM policy to establish histocompatibility between donor and recipient (Taylor et al., 2010).

In comparison, pXM requires the presence of H&I staff, donor tissues and recipient serum sample to initiate crossmatching. The process takes 4 hours on average to complete. Waiting for donor tissues (spleen, lymph nodes) to arrive following retrieval surgery and for recipients to arrive at transplant centre before obtaining recipient sample add to the delay. This could be mitigated by the use of lymphocytes isolated from donor peripheral blood sample that was obtained prior to retrieval surgery for tissue typing and thus eliminating the need to wait for donor tissues to be delivered. Additionally, pXM could be commenced earlier if a historic recipient serum sample is used where suitable. Recipient's historic serum sample without a recent sensitising event is sufficient for pXM and negates the need to await recipient arrival at transplant centre to provide a fresh sample (Bryan, 1991). Only 21% of the transplants that required pXM used donor pre-retrieval peripheral blood and only 35% used historic recipient serum for histocompatibility testing. CIT, in this group,

could be reduced by a median of 3 hours simply by using pre-retrieval peripheral blood for crossmatching. Evidently, obtaining donor and recipient samples as early in the donor process as possible is key to reducing CIT significantly in both DBD and DCD transplants and hence, there is still a large scope to implement this practice more widely (Inotai et al., 2012, Elgueta et al., 2010).

When recipients required haemodialysis immediately pre-transplant it only significantly impeded transplants in vXM group but did not affect those that required pXM. It may be possible that haemodialysis where required overlapped the time when pXM was being performed. As the decision to proceed with a vXM was made very early, often before retrieval surgery, any additional time including that for haemodialysis could delay transplants. Early recipient contact and their preparation for transplant, especially those who require haemodialysis, is likely to shorten CIT in the vXM group.

There were still significant delays in both pXM and vXM groups despite confirmation of histocompatibility, arrival of kidney and completion of recipient preparation including haemodialysis where required suggesting there were other contributing factors.

Factors attributing that were common to both groups were kidney transport time, reallocation of kidneys and access to theatre.

There was a positive correlation between distance travelled by retrieved kidneys from 122 donor hospitals to 22 recipient transplant centres and their CITs. This was significant when the travel distance was above 100 miles. Kidney transport time, especially those beyond 4 hours, significantly impacted CIT in both pXM and vXM groups. However, although kidneys that were transported by air travelled the furthest distance (median 300 miles) their CITs were not significantly different to those transported by road (Blackmur, 2013). There is a clear advantage in transporting kidneys by air when travel distance is beyond 200 miles to shorten travel time. Positive correlation between kidney travel distance and CIT has also been shown previously in a large-scale survey of UNOS data (Salahudeen and May, 2008). Reasons for delays in transporting kidneys varied, with most delays occurring due to traffic congestion or decline by transplant centres and consequent change of destination and reallocation. Some of the other reasons were loss of communication, vehicle breakdown, delay in accepting offered kidney and lack of suitable transport. Kidney reallocation was one of the most significant factors adversely affecting CIT that is common to both the groups. Although the number of reallocated kidneys was small, it added an average of 4 hours to CIT. It was previously shown that CIT increased by an average of 7 hours each time a kidney offered through the national allocation scheme if initially accepted by a transplant centre for it to subsequently be transplanted in a different patient (Johnson et al., 2010b). There is a clear need to keep reallocation to the minimum and, if needed, to make the decision before the kidney leaves donor hospital to avoid unwarranted extra transport time. In majority of the cases it is attributed to recipients being unfit for transplantation at the time of offer. This highlights the need for regular assessment and notification of any illness



for wait-listed patients to avoid reallocation to a different patient. In SPK transplants, 15% of pancreas had to be discarded because of unsuitability or damage to the organ and the kidneys were reallocated to different recipients. Thorough assessment of the pancreas for suitability for transplant at the time of retrieval would decrease the incidence of such reallocation.

Data for recipient preparation and theatre activities were limited. There was a 3-hour delay for transplant surgery to start, despite XM result, kidney and recipient being ready. Evidently, factors relating to availability of theatre, anaesthetists, surgeons and theatre staff also had an impact on CIT. An early part of the study included interrogation of staff and survey of logistics and local practices at all renal transplant units in the UK. As shown in previous studies, lack of a dedicated theatre for transplant was identified as the major rate-limiting factor (Seow et al., 2006, Elgueta et al., 2010, Vacher-Coponat et al., 2007). The majority (76%) of transplants were performed in emergency theatres and CIT for transplants that were performed in a dedicated transplant theatre was significantly shorter. Reasons most commonly identified for this include vying for theatre space with emergency cases and availability of anaesthetists and theatre staff. Significant number of transplants occurs out of hours when there is limited access to theatre and fewer theatre staff and anaesthetists at night times and during weekends (Seow et al., 2006). A change in policy prioritising adequate theatre access at all hours should be pursued and implemented to keep CIT to a minimum.

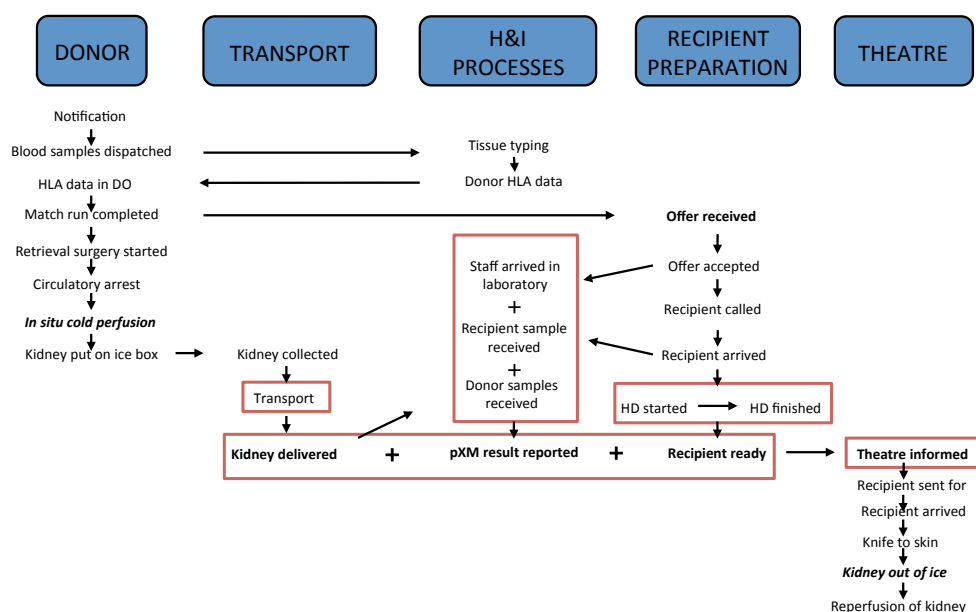
The data collected for H&I, donor activities and kidney transport were comprehensive, making the relevant findings highly significant. One of the limitations of the study is the paucity of data surrounding activities at transplant centres relating to recipient, theatre and surgical factors. The structure and logistics of the recipient transplant centres were varied and complex, involving numerous members of the clinical team. Collection of information for the activities depended on individual members of the clinical team who provided 32-35% of data for recipient and theatre activities in the study. This was supplemented by information collected by interviewing members of the staff at all centres early in the study process. Although this data was limited, the study has identified significant factors that remain pertinent.

An alternative method that could be used to analyse data in the study is comparing transplants between DBD and DCD donors. A multivariate model incorporating the categorical and continuous factors that were found to be significant in the two groups could then be developed for multivariate analysis.

With the increasing use of newer alternative organ preservation techniques such as hypothermic machine perfusion and normothermic regional perfusion, static cold storage technique may become less universal. However, as these techniques are still evolving and cold storage remains the principal method for kidney preservation and transport between donor hospital and recipient transplant centre, CIT remains an important factor in deceased donor transplantation (Hameed et al., 2016, Lam et al., 2013).

Figure 4.1 shows some of the important areas for intervention to make gains in the overlapping events in the kidney timeline.

**Figure 4.1 Logistical areas for possible intervention to reduce CIT**



1. All centres should adopt a vXM policy and use vXM in as many transplants as possible.
2. One of the novel measures that could be utilised in this era of modern technologies is to introduce tracking system for the organs in collaboration with the transport providers that will provide real-time tracking of the organs so that preparation of recipients, staff and theatre could be carried out in a more efficient and timely manner to minimise delays.

3. Recipients requiring HD immediately pre-transplant should be identified earlier in the process and HD should be started sooner to limit delay.
4. There should be a dedicated theatre for transplants in each centre so that there is sufficient and timely access to theatre for transplants to take place as this has been identified as one of the significant rate-limiting factors when kidney, recipient and XM result are ready for transplants to proceed.

## 4.1 Summary

The logistics of deceased donor kidney transplantation are complex and multifactorial, encompassing coordinated efforts between various specialities and personnel across the UK for the best possible outcome. CIT is recognised as one of the principle and potentially modifiable factors that can lead to better transplant outcomes. The study sought to comprehensively investigate the process to identify areas for delay along the course of kidney journey with a view for expediting the process, where possible, to shorten the journey and consequently, CIT.

Introduction of a vXM policy where suitable was the crucial factor identified to shorten CIT, and efforts should be made to adopt and increase the practice. Earlier recipient contact for those who require haemodialysis immediately before transplant and are suitable to proceed with a vXM, and use of donor pre-retrieval peripheral blood and historic recipient serum sample for crossmatching for those requiring pXM can reduce CIT further. Access to dedicated transplant theatre round the clock, minimising reallocation of kidneys and using faster mode of transport for kidneys if distance is greater than 100 miles can also expedite the process

The possible introduction to opt out legislation for deceased organ donation in Scotland and England will also have an impact on organ donor numbers. Therefore, an appreciation of the logistical challenges is of vital importance.

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## Logistical Factors Influencing Cold Ischemia Times in Deceased Donor Kidney Transplants

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**Background.** Prolonged cold ischemia time (CIT) is associated with a significant risk of short- and long-term graft failure in deceased donor kidney transplants across the world. The aim of this prospective longitudinal study was to determine the importance of logistical factors on CIT. **Method.** Data on 1763 transplants were collected prospectively over 14 months from personnel in 16 transplant centers, 19 histocompatibility and immunogenetics laboratories, transport providers, and National Health Service Blood and Transplant. **Results.** The overall mean CIT was 13.8 hours, with significant center variation ( $P < 0.0001$ ). Factors that significantly reduced CIT were donation after circulatory death ( $P = 0.03$ ), shorter transport time ( $P = 0.0002$ ), use of virtual crossmatch (XM) ( $P < 0.0001$ ), and use of donor blood for pretransplant XM ( $P < 0.0001$ ). The CIT for transplants that went ahead with a virtual XM was 3 hours shorter than those requiring a pretransplant XM ( $P < 0.0001$ ). There was a mean delay of 3 hours in starting transplants despite organ, recipient, and pretransplant XM result being ready, suggesting that theater access contributes significantly to increased CIT. **Discussion.** This study identifies logistical factors relating to donor, transport, crossmatching, recipient, and theater that impact significantly on CIT in deceased donor renal transplantation, some of which are modifiable; attention should be focussed on addressing all of these.

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Delayed graft function (DGF), which can be defined as the requirement for dialysis in the first 7 days after transplantation, occurs in a significant number of deceased donor (DD) renal transplants, cited as between 25% and 50%,<sup>1</sup> and is associated with a significantly increased risk of graft loss over the years after transplantation, higher serum creatinine at 1 year, and an increased risk of acute rejection.<sup>2</sup> Risk factors

for DGF include cold ischemia time (CIT), donor factors, such as age and serum creatinine, recipient factors, such as body mass index, and immunological and logistical factors.<sup>3</sup> Of these, prolonged CIT has been shown to be the most significant individual factor in predicting DGF: Irish et al<sup>4</sup> reported that for every hour of increased CIT, there was a 4% increased risk of DGF. Cold ischemia time is defined as the time from commencement of cold perfusion at the time of donor surgery to the removal of the kidney from ice in the recipient center and is affected by a complex logistical pathway that includes kidney allocation, transport, crossmatching, preparation of the recipient, and access to theater.

Kidneys that are particularly susceptible to ischemic damage and DGF are those from DDs after circulatory death (DCD), and extended criteria donors (older >60 years) donors and those with comorbidities, for example, cardiovascular disease).<sup>5</sup> With increasing numbers of patients waiting for transplantation, more such organs are accepted and thus CIT will remain an important consideration in DD transplantation.<sup>6,7</sup> We prospectively studied the impact of individual logistical factors on CIT, relating to events from the time of kidney retrieval at the donor hospital to kidney being removed from ice in the recipient center (Figure 1). Although logistical details vary between nations and organ sharing schemes, our findings are worthy of careful reflection internationally.

### MATERIALS AND METHODS

#### Data Collection

Prospective data collection was performed between June 2011 and the end of July 2012. Before commencement of the data collection, all United Kingdom transplant centers,

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S.S.S. performed the research. L.B. participated in data analysis. M.B. and J.B. helped to perform the research. C.W. participated in research design. C.T. participated in research design and in writing the paper. J.F. participated in research design and in writing the article. R.J. and L.M. participated in research design, in data analysis and in writing the article.

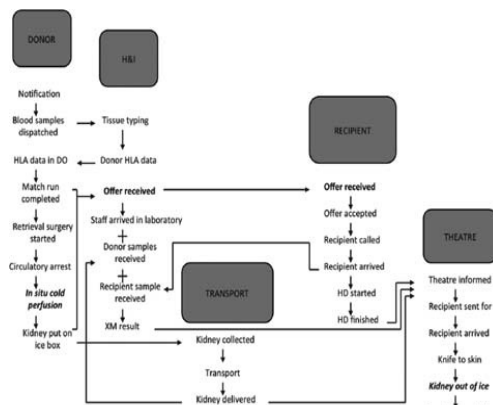
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**FIGURE 1.** Logistics of deceased donor transplantation in the United Kingdom. DO indicates duty office; HD, hemodialysis.

specialist nurses for organ donation and histocompatibility and immunogenetics (H&I) laboratories were visited to maximize participation with the study. The study was funded from a research grant from National Health Service Blood and Transplant (NHSBT), and was approved by the Kidney Advisory Group, which advises NHSBT on all aspects of kidney transplantation within the United Kingdom. Staff involved in the data collection included specialist nurses for organ donations, H&I staff, transport providers, recipient transplant coordinators, transplant surgeons/fellows/specialist registrars, nephrologists, theater and ward staff, and NHSBT.

Data were obtained on DD kidney only and simultaneous pancreas and kidney (SPK) transplants from 16 of the 22 invited transplant centers (6 centers declined to participate) along with all 19 H&I laboratories (supporting all 22 transplant centers), with the aim of determining whether there are specific areas on which to focus efforts to reduce CITs. The CIT was calculated from United Kingdom Transplant Registry data held by NHSBT and was defined as the time from in situ cold perfusion in donor at the time of retrieval to the time of removal of kidney from ice for transplantation in recipient. This was available for all transplants performed in all 22 centers.

Factors that were considered to be relevant for this study were agreed with a national multidisciplinary team, including transplant surgeons, H&I scientists, and statisticians. In addition, draft documents were circulated to the heads of transplant centers for their input. Categorical and continuous data were collected along the kidney timeline from the time of organ donation at the donor hospital to completion of transplantation at recipient hospital on four different data collection forms. We focused on 5 key logistical areas, namely, donor operation, organ transport, laboratory tests, including the match run and the crossmatch (XM), recipient preparation and theater, as shown in Figure 1. For clarity, the duty office at NHSBT performs the match run once the donor HLA type is known; this is matched to the recipient pool. We examined different factors within each of these key areas to identify those that impacted on CIT.

A national database was set up, and data input was done prospectively. Data were checked for errors, and each outlier was examined by rechecking them against the original forms as well as with the rest of the data for the corresponding transplant. We excluded transplants that did not proceed

despite retrieval of organs, and kidneys that were transplanted with organs other than pancreas. When 2 kidneys were transplanted in a single recipient (double kidney transplant), the one with the longer CIT was excluded. Data on recipient and theater times that were inconsistent with the rest of the data and those that had a discrepancy of more than 1 hour from NHSBT data were excluded ( $n = 52$  transplants). Transplants with no virtual crossmatch (vXM) or pretransplant XM (pXM) information were excluded. Data cleansing was undertaken before the final analysis: 5% of the data were selected randomly at regular intervals, and each one was checked against the original forms and records to establish excellent quality assurance of the input data. An error rate less than 1% was considered acceptable. Data were collected for almost 100% of donor and H&I data for that period, with 37% of transport data, 32% of recipient, and 35% of theater data from the 16 participating centers.

### Crossmatch Terminology

Several centers in the United Kingdom have adopted selective omission of the pXM in potential recipients who are at low immunological risk,<sup>8</sup> and this has been shown to be safe and effective at reducing CIT.<sup>9</sup>

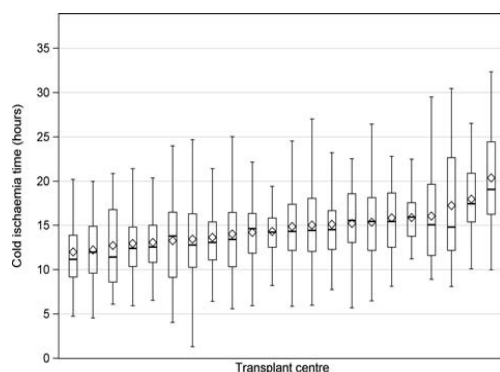
For clarification in this study, we will use the term pXM for those transplants that required full XM testing to be performed before start of surgery, and vXM for those in whom the prospective pretransplant donor XM was omitted and it was safe to proceed without waiting for the XM test to be performed. The formal XM test was performed retrospectively, and there have been no cases of unexpected XM positivity after transplantation.

### Statistical Analysis

General demographics of DD kidney and SPK transplantation in the 14-month period included number and type of donors, kidneys, transplants, recipients, allocation, and reallocation across the United Kingdom transplant centers. All relevant time intervals were collected in hours. Various time intervals between donor notification and completion of transplant surgery were examined, namely, times of retrieval surgery, transport of organs, donor HLA typing and crossmatching, recipient preparation and transplant theater. Donor-related categorical data included in the analyses were type of donor (donation after brain death [DBD] or DCD) and donor tissues used for crossmatching. Transport-related categorical data was mode of organ transport, H&I-related data were type of crossmatching, types of donor tissues and recipient blood samples used if pXM test done, recipient-related categorical factors included mode of recipient travel to the transplant center, requirement for haemodialysis immediately before transplant and requirement for current recipient serum sample for crossmatching. The sole theater-related categorical factor included was whether the transplant was performed in an emergency or transplant-dedicated theater.

All data within the study period were included in the univariate analysis. Parametric tests were performed to assess differences in CIT across transplant centers and XM type, variation in XM across transplant centers and variation in practice around the use of donor samples for pXM. A general linear model was used to determine the contributions of various factors and time intervals to the CIT. Because of the





**FIGURE 2.** There was significant variation in CIT between centers across the United Kingdom, expressed as box and whisker plot with mean. The shortest mean CIT was 12.00 hours and the longest of 20.36 hours, compared in all 22 centers ( $F = 10.060$ ,  $P < 0.0001$ ).

missing data, time intervals were analyzed categorically. The distribution of each of the time intervals was used to decide appropriate categories. Factors that were found to be significant in the univariate analyses were incorporated in the multivariate modelling. Only significant factors in the multivariate modelling were included in the final model.

$P$  values less than 0.05 were considered significant. All analyses were performed using SPSS version 19, IBM, UK, and SAS version 9.4.

#### Intercept Description

The intercept is the median CIT if all other factors are set to zero (the baseline).

### RESULTS

#### General Demographics

Data include information for 1763 single/double/en-bloc kidney only and SPK transplants from across the United Kingdom. Of those, 1586 (90%) were kidney only and 177 (10%) SPK transplants. Fifty-five of the 1586 kidney

only transplants were double and 4 were en-bloc kidney transplants. The DCD kidneys constituted more than a third (41%) of the transplants, and the majority of kidneys (64%) were shipped between centers. Forty-three (2%) kidneys were reallocated: 32 were reallocated locally, and 11 were reallocated to a different transplant center.

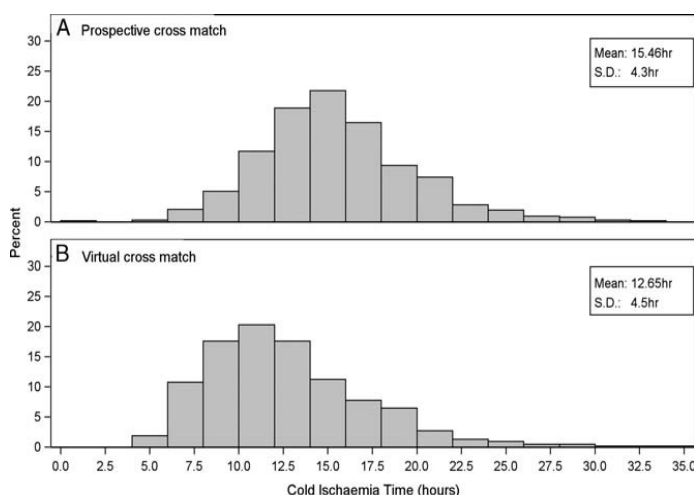
#### Cold Ischemia Times

The overall mean CIT for kidney transplants in all transplant centers was 13.8 hours [SD, 4.5; Interquartile range (IQR) 10.7-16.4]. The shortest recorded CIT was 3.7 hours, and the longest was 33.1 hours.

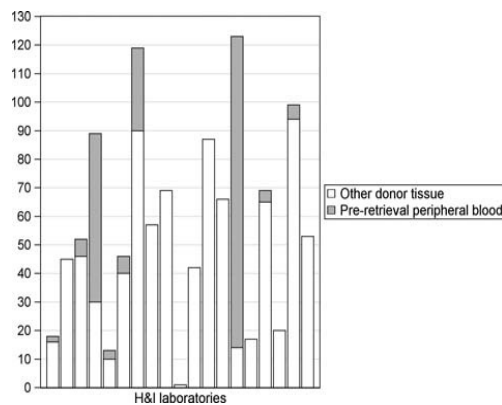
There was significant center variation in mean CIT ranging between the shortest of 12.0 hours and the longest of 20.4 hours in the 22 centers ( $F = 10.060$ ,  $P < 0.0001$ ), as shown in Figure 2.

The most significant factor affecting CIT overall was the adoption of a vXM policy. Transplants that required a pXM had a CIT that was 3 hours longer than those where the XM test was omitted and proceeded directly to transplant based on a negative vXM (Figure 3,  $P < 0.0001$ ). There was significant center variation in the number of transplants performed using vXM; indeed at the time of the study two centers had not adopted a vXM policy ( $P < 0.0001$ ). Because of the key role played by the type of XM performed and the fact that the kidney pathway diverges depending on whether the transplant requires a pretransplant crossmatch or not, the analysis was performed separately for vXM and pXM groups.

If a pXM is required, this can be performed using donor peripheral blood obtained preretrieval, or lymph node and spleen that are taken at the time of retrieval and accompany the organs to the recipient center. We sought to determine whether there was variation in practice with regard to the use of donor tissue for pXM because this was likely to significantly alter the timing of availability of the XM result. There were significant differences in laboratory practice, with 1 laboratory performing approximately 89% pXM on peripheral



**FIGURE 3.** The impact of the crossmatch type on CIT; transplants that proceeded based on a virtual cross match (omitting the pre-transplant crossmatch test) had a median CIT of approximately 3 hours less than those that required a prospective cross match. ( $t$  test,  $P < 0.0001$ ). A, Pretransplant cross match. B, Virtual cross match.



**FIGURE 4.** Laboratory variation in practice around use of donor samples for pretransplant crossmatch.

blood, whereas other laboratories were dependent on the arrival of lymph nodes and spleen in all cases (Figure 4).

The factors that were included in a univariate analysis for both vXM and pXM groups are outlined in Table 1 (categorical) and Table 2 (continuous). These include factors pertaining to each stage of the kidney journey from donor to recipient, and key timelines of the process.

#### Factors Affecting CIT in Transplants Requiring pXM Test (Univariate Analysis)

In the pXM group, several factors contributed significantly to CIT in univariate analysis: CIT was significantly shorter in DCD transplants than DBD ( $P = 0.0003$ ); kidneys that were transplanted locally had a shorter CIT than those that were exported ( $P < 0.0001$ ), and CIT was prolonged if

kidneys were reallocated either locally or to a second center ( $P = 0.0007$ ). Importantly, if the pXM was performed using donor peripheral blood obtained before start of retrieval, rather than donor lymph nodes and spleen obtained at retrieval and transported with the organs, CIT was significantly reduced ( $P < 0.0001$ ). Similarly, if stored recipient blood was available for crossmatching purposes, this resulted in a significant reduction in CIT ( $P < 0.0001$ ). Continuous variables that were found to contribute to CIT in the pXM group were transport times, time taken from in situ cold perfusion to the kidney boxed ready for transport, time between the offer made and the kidney accepted by the recipient center, and time to obtain the XM result. Once the kidney had arrived and pXM result is known, any further delay in proceeding with the transplant was documented and was found to have a significant impact on CIT.

#### Factors Affecting CIT in Transplants Undertaken Using vXM (Univariate Analysis)

Significant factors in univariate analysis were donor type (DBD/DCD) ( $P = 0.01$ ), and whether the kidney was allocated locally or imported from another region ( $P = 0.04$ ). In the small number of kidneys that were reallocated, this had a significantly detrimental impact on CIT ( $P < 0.0001$ ). Requirement for recipient hemodialysis before transplantation also had a significant impact ( $P = 0.003$ ). Continuous factors that were relevant included timing from cold perfusion to kidney boxed ready for transport, offer accepted to contacting the recipient, timing of kidney collection, and its transport.

#### Multivariate Analysis of Factors Affecting CIT

All factors that were significant in univariate analyses were considered in multivariate modelling, and factors that

**TABLE 1.**

**Categorical factors included in the univariate analysis for pXM and vXM groups**

Factor	Level	Pretransplant crossmatch		Virtual crossmatch		Total	
		N	%	N	%	N	%
Donor type	DBD	703	62	333	52	1036	59
	DCD	424	38	303	48	727	41
Local	No	740	66	390	61	1130	64
	Yes	387	34	246	39	633	36
Reallocated kidney	No/unknown	1104	98	616	97	1720	98
	Yes	23	2	20	3	43	2
Peripheral blood	No	867	79	—	—	867	79
	Yes	224	21	—	—	224	21
	Missing	36	—	—	—	36	—
Current sample	No	389	35	—	—	389	35
	Yes	709	65	—	—	709	65
	Missing	29	—	—	—	29	—
Recipient mode of travel to hospital	Ambulance	20	6	13	5	33	5
	Air	0	0	4	2	4	1
	Patient's own	286	81	205	77	491	79
	Taxi	46	13	44	17	90	15
	Other	1	<1	0	0	1	<1
	Missing	774	—	370	—	1144	—
Hemodialysis required by recipient	No	261	71	186	67	447	—
	Yes	106	29	91	33	197	—
	Missing	760	—	359	—	1119	—

Local: when a kidney, retrieved at one of the hospitals within a defined geographical region, is transplanted at the designated transplant unit for that region.

Reallocation: when a kidney, which was initially accepted for transplantation in a particular recipient at a transplant unit, is subsequently allocated to a second recipient at the same or a different hospital.

**TABLE 2.****Continuous factors included in the univariate analysis for pXM and vXM groups**

Factor	Pretransplant crossmatch, h			Virtual crossmatch, h		
	N	Median	IQ range	N	Median	IQ range
Cold perfusion to kidney in ice box	867	1.27	1.02-1.55	475	1.28	1.02-1.62
Offer accepted to latest of staff in lab, donor sample arrive, or recipient sample arrive	308	9.42	6.20-13.00	—	—	—
Offer accepted to agreement to proceed with a vXM	—	—	—	197	3.00	1.13-6.33
Offer accepted to recipient contacted	292	1.80	0.33-6.58	222	2.63	0.65-6.25
Recipient contacted to recipient arrived	307	2.00	1.33-3.00	240	2.00	1.50-3.00
Kidney on ice to kidney collected	405	0.93	0.67-1.25	201	1.00	0.67-1.42
Kidney collected at donor hospital to kidney delivered to recipient center	426	1.83	1.08-3.17	221	2.17	1.33-3.42
Matching run complete to pXM result	1100	14.42	10.52-19.02	—	—	—
Matching run complete to agreement to proceed with a vXM	—	—	—	494	4.43	1.60-9.17
Latest (XM result known, organ delivered) to transplant surgery started	342	3.30	2.28-5.17	82	3.82	2.53-6.00
Transplant surgery started to kidney out of ice	354	0.90	0.65-1.25	264	0.87	0.70-1.22

remained significant are shown in Table 3. Key findings in the pXM group are shown in Table 3A: if peripheral blood is used for pXM, CIT is reduced by more than 3 hours. Factors

that led to an increased CIT are travel times (adding between 1.5 and 2.3 hours) or kidney reallocation (+2.6 hours). In addition, once the kidney had arrived and the pXM result was

**TABLE 3.****Multivariate analysis of factors affecting cold ischemia time for (A) pXM group and (B) vXM group**

Factor	Level	Estimated change in CIT, h	Standard error	P
<b>(A) Pretransplant crossmatch</b>				
Intercept		13.3	0.4	<0.0001
Peripheral blood	No	Baseline		
	Yes	-3.4	0.3	<0.0001
Kidney collected to kidney delivered	Less than 2 h	Baseline		
	2-4 h	1.5	0.5	0.0007
	More than 4 h	2.3	0.6	0.0002
	Missing	1.3	0.3	<0.0001
Kidney reallocated	No	Baseline		
	Yes	2.6	0.8	0.0019
Cold perfusion to kidney on ice	Less than 1 h 30 min	Baseline		
	More than 1 h 30 min	1.1	0.3	0.0004
	Missing	0.7	0.3	0.02
Latest (XM result known, organ delivered) to transplant surgery started	Less than 5 h	Baseline		
	5-9 h	2.1	0.5	<0.0001
	More than 9 h	5.7	1.0	<0.0001
	Missing	1.5	0.3	<0.0001
<b>(B) Virtual crossmatch</b>				
Intercept		8.7	0.7	<0.0001
Donor type	DCD	Baseline		
	DBD	0.8	0.4	0.03
Recipient on HD	No	Baseline		
	Yes	1.3	0.6	0.02
	Missing	1.3	0.4	0.002
Kidney reallocated	No	Baseline		
	Yes	5.7	1.0	<0.0001
Kidney collected to kidney delivered	Less than 2 h	Baseline		
	2-4 h	1.6	0.6	0.01
	More than 4 h	2.8	0.9	0.002
	Missing	1.8	0.5	0.0004
Latest (proceed with vXM, organ delivered) to transplant surgery started	Less than 5 h	Baseline		
	5-9 h	2.7	1.1	0.01
	More than 9 h	7.6	1.7	<0.0001
	Missing	0.8	0.7	0.2

Explanation of "intercept" is provided in the Methods section.

known, a further delay in start of surgery had a significant detrimental impact on CIT. This was also significant in the context of the vXM group (Table 3B), leading to a significant delay in commencement of surgery and thus increasing CIT. Other factors that remained significant in the vXM group were the patient requiring hemodialysis before transplantation, travel time, and kidney reallocation.

## DISCUSSION

Cold ischemia time is one of the few modifiable factors that have been identified as a significant risk factor for DGF, with long-term implications for graft survival in DD renal transplants.<sup>2,10-12</sup> It is likely that, in the current era of accepting kidneys from extended criteria donors, and DCD donors, CIT will continue to play a significant role, and should be minimized, as evidenced by the experience of the Eurotransplant Senior program.<sup>13</sup>

We have examined logistical factors that contribute to CIT in the context of national (DBD) and regional (DCD) allocation of DCD kidneys within the United Kingdom. Organ retrieval, transport, and implantation logistics vary between countries and organ sharing networks; however, studies examining these are lacking, despite a clear need for such investigation.<sup>14</sup> Thus, we consider the international relevance of factors identified in this study based on current literature available. One regional French study examining the impact of the introduction of a timesheet on CIT in locally and nationally allocated kidneys found that the introduction of such a time sheet alone reduced CIT from 21 hours to 13 hours in a case control study.<sup>15</sup> Another review of factors affecting CIT in Chile highlighted the impact of kidney sharing, reallocation, and factors pertaining to HLA typing and crossmatching.<sup>16</sup>

The factor that contributed most significantly to CIT was the introduction of a vXM policy in patients that were deemed suitable for such: these patients have low immunological risk, with known HLA antibody profile and few unacceptable antigens. This finding requires further interrogation: the prolonged CIT in patients requiring a pXM may be due to other factors relating to their more complex sensitisation profiles. A study from Cambridge demonstrated that the introduction of a virtual crossmatch policy in carefully selected patients could be undertaken safely and leads to an effective reduction in CIT.<sup>8,9</sup>

It is likely that lessons can be learned internationally from this finding. In the United States, virtual crossmatching is adopted to predict whether or not a kidney should be shipped to a distant center for transplantation into a sensitized patient, but the pXM is still performed on arrival of the kidney at the recipient center. A review of this policy with the introduction of a vXM policy is likely to lead a reduction in CIT, and might be safely introduced.<sup>9</sup> However, introduction of a vXM policy does not always result in reduced CIT, as has been shown recently in a Swiss study: the policy led to improved allocation, reduced workload on the H&I staff, and improved risk stratification for modified immunosuppression, but CIT was the same in both groups.<sup>17</sup>

Factors that were common to both pXM and vXM groups were travel time, kidney reallocation, and a delay in gaining access to theater, despite the availability of the XM result and the kidney having arrived at the recipient hospital. When members of staff were interviewed at all transplanting centers across the United Kingdom as an early part of this work, the

most commonly perceived reason for prolonged CIT was lack of access to theater, due to competing interests of emergency cases, and availability of anesthetic and theater staff. It has been previously shown that more than 50% of kidney transplants are performed overnight and at weekends when there are fewer operating rooms and less staff coverage (nursing, anaesthetic)<sup>18</sup> and we must implement policy changes that prioritize sufficient theater access out of hours if we are to continue to strive to minimize CIT and optimize outcomes.

One limitation of the study is the paucity of data relating to transport, recipient, and surgical factors. The study relied on information being collected by individual members of the clinical team at the recipient hospital, resulting in approximately 33% data being collected. Formal collection of transport times has now been built into the contract of transport providers. Despite this shortcoming, significant and important factors have been identified, which remain relevant.

With the introduction of novel technologies that aim to improve perfusion and organ preservation, such as machine perfusion and normothermic regional perfusion, static cold storage may become a less commonly adopted technique. However, although organs continue to be transported on ice between centers to optimize transplant outcomes, CIT remains an important factor. This study has demonstrated specific logistical factors that can be addressed with the potential to minimize CIT further and has international relevance because CIT is recognized as a key factor contributing to DGF.

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## Appendix 2: SE Scotland Research Ethics Service approval

### South East Scotland Research Ethics Service

Waverley Gate  
2-4 Waterloo Place  
Edinburgh  
EH1 3EG



Name: Lorna Marson  
Address: Senior Lecturer  
in Transplant Surgery  
University of Edinburgh  
Edinburgh

Date: 20/04/2011  
Your Ref:  
Our Ref: NR/1104AB6  
Enquiries to: Alex Bailey  
Direct Line: 0131 465 5679  
Email: alex.bailey@nhslothian.scot.nhs.uk

Dear Lorna,

**Full title of project: Minimising Cold Ischaemia to Maximise Outcomes in Deceased Donor Kidney Transplants**

You have sought advice from the South East Scotland Research Ethics Service on the above project. This has been considered by the Scientific Officer and you are advised that, based on the submitted documentation (SN-OD e-form.doc, Recipient Coordinator e-form.doc, CIT Research Proposal.doc), the first section (Examination of factors affecting cold ischaemic times across the United Kingdom) does not need NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees in the UK. The advice is based on the following:

- *The project is an audit using only data obtained as part of usual care, but note the requirement for Caldicott Guardian approval for the use or transfer of person-identifiable information within or from an organisation*

I advise that sections 2 and 3:

Pilot study of modifications to factors influencing cold ischaemic times  
Study of impact of the changes on cold ischaemic times

do require NHS ethics review.

This letter should not be interpreted as giving a form of ethical approval or any endorsement of the project, but it may be provided to a journal or other body as evidence that ethical approval is not required under NHS research governance arrangements. However, if you, your sponsor/funder or any NHS organisation feels that the project should be managed as research and/or that ethical review by a NHS REC is essential, please write setting out your reasons and we will be pleased to consider further. Where NHS organisations have clarified that a project is not to be managed as research, the Research Governance Framework states that it should not be presented as research within the NHS.

You should retain a copy of this letter with your project file as evidence that you have sought advice from the South East Scotland Research Ethics Service.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Alex Bailey'.

Alex Bailey  
Scientific Officer  
South East Scotland Research Ethics Service

## South East Scotland Research Ethics Service

### DIFFERENTIATING AUDIT, SERVICE EVALUATION AND RESEARCH

November 2006

The "Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees" recommended NRES should develop guidelines to aid researchers and committees in deciding what is appropriate or inappropriate for submission to RECs, and NRES (with the Health Departments and with advice from REC members) has prepared the guidelines in the form of the attached table.

RESEARCH	CLINICAL AUDIT	SERVICE EVALUATION
The attempt to derive generalisable new knowledge including studies that aim to generate hypotheses as well as studies that aim to test them.	Designed and conducted to produce information to inform delivery of best care.	Designed and conducted solely to define or judge current care.
Quantitative research – designed to test a hypothesis. Qualitative research – identifies/explores themes following established methodology.	Designed to answer the question: “Does this service reach a predetermined standard?”	Designed to answer the question: “What standard does this service achieve?”
Addresses clearly defined questions, aims and objectives.	Measures against a standard.	Measures current service without reference to a standard.
Quantitative research -may involve evaluating or comparing interventions, particularly new ones. Qualitative research – usually involves studying how interventions and relationships are experienced.	Involves an intervention in use ONLY. (The choice of treatment is that of the clinician and patient according to guidance, professional standards and/or patient preference.)	Involves an intervention in use ONLY. (The choice of treatment is that of the clinician and patient according to guidance, professional standards and/or patient preference.)
Usually involves collecting data that are additional to those for routine care but may include data collected routinely. May involve treatments, samples or investigations additional to routine care.	Usually involves analysis of existing data but may include administration of simple interview or questionnaire.	Usually involves analysis of existing data but may include administration of simple interview or questionnaire.
Quantitative research - study design may involve allocating patients to intervention groups. Qualitative research uses a clearly defined sampling framework underpinned by conceptual or theoretical justifications.	No allocation to intervention groups: the health care professional and patient have chosen intervention before clinical audit.	No allocation to intervention groups: the health care professional and patient have chosen intervention before service evaluation.
May involve randomisation	No randomisation	No randomisation
ALTHOUGH ANY OF THESE THREE MAY RAISE ETHICAL ISSUES, UNDER CURRENT GUIDANCE:-		
RESEARCH REQUIRES R.E.C. REVIEW	AUDIT DOES NOT REQUIRE R.E.C. REVIEW	SERVICE EVALUATION DOES NOT REQUIRE R.E.C. REVIEW

## **Appendix 3: – Questionnaire for specialist nurse for organ donation (donation information)**

**National Audit of CIT**

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### **Kidney Donation and Retrieval Information**

#### **For attending Specialist Nurse for Organ Donation (SN-OD)**

#### **Notes:**

1. Please complete this form for every deceased donor.
2. This form can be completed either manually or electronically.
3. The study coordinator will greatly appreciate it if you could complete this form as clearly as possible and with black ink only.
4. When complete, please return the form to the coordinator centre in one of the following ways:

**Post:**

Sussie Shrestha  
C/O Ms Lorna Marson  
Consultant Surgeon  
Royal Infirmary of Edinburgh  
51 Little France Crescent  
Edinburgh  
EH16 4SA

**Fax No:** 0131 242 3617

**Email:** [sussie.shrestha@nhs.net](mailto:sussie.shrestha@nhs.net)

4. If you have any queries, please do not hesitate to contact the study coordinator, Ms Sussie Shrestha, on **07875500726 (mobile)**.



**Study: Minimising cold ischaemia to maximise outcomes in deceased donor kidney transplants**

**PI: Ms Lorna Marson, University of Edinburgh, Royal Infirmary of Edinburgh, EH16 4SA**

This national audit will investigate factors influencing cold ischaemia times (CIT) in deceased donor kidney and kidney/pancreas transplantation in the UK with the aim of modifying practice to minimise CIT where possible. The study requires supplementary data collection from H&I staff and recipient coordinators to capture the complete journey of each kidney. In addition to data already collected on the Kidney Donor Information form, please provide the date/time requested below FOR EACH DECEASED KIDNEY DONOR and stick this label to the corresponding Kidney Donor Information Form for return to ODT. Many thanks for your assistance.

Donor ID \_\_\_\_\_

Date/time blood samples dispatched to H&I (date) \_\_/\_\_/20\_\_ (time 24 hrs) \_\_:\_\_:\_\_

Date of Referral (dd/mm/yyyy):		
<b>DONOR DETAILS</b>		
ODT Donor No:		
Type of Donor:	DBD <input type="checkbox"/>	DCD <input type="checkbox"/>
<b>DONOR HOSPITAL</b>		
Hospital name:		
Date retrieval started (dd/mm/yyyy):		
	<b>Date (dd/mm/yyyy)</b>	<b>24hrTime(hh:mm)</b>
Time blood samples dispatched to H&I		
Time of circulatory arrest		
Time of in situ cold perfusion		
Time kidney on ice box <b>RIGHT</b> kidney		
Time kidney on ice box <b>LEFT</b> kidney		
Kidney collection time <b>RIGHT</b> kidney		
Kidney collection time <b>LEFT</b> kidney		
<b>Reason for delay if any:</b>		

**Form completed by (please print):**

## Appendix 4: Questionnaire for Histocompatibility and Immunogenetics staff (HLA crossmatching information)

National Audit of CIT

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### HLA Crossmatching Information

For attending H&I Staff

#### Notes:

1. Please complete this form for each recipient of a deceased donor kidney and kidney + pancreas transplant.
2. This form can be completed manually or electronically.
3. The study coordinator will greatly appreciate it if you could complete this form as clearly as possible and with black ink only.
4. When complete, please return the form to the coordinator centre in one of the following ways:

**Post:**

Sussie Shrestha  
C/O Ms Lorna Marson  
Consultant Surgeon  
Royal Infirmary of Edinburgh  
51 Little France Crescent  
Edinburgh  
EH16 4SA

**Fax No:** 0131 242 3617

**Email:** [sussie.shrestha@nhs.net](mailto:sussie.shrestha@nhs.net)

5. If you have any queries, please do not hesitate to contact the study coordinator, Ms Sussie Shrestha, on **07875500726 (mobile)**.

Date (dd/mm/yyyy):
<b>DONOR DETAILS</b>
ODT Donor No:
Local <input type="checkbox"/> Import <input type="checkbox"/>
<b>H&amp;I LABORATORY</b>
Location of Laboratory:
<b>RECIPIENT DETAILS</b>
Patient Transplant Centre:

<b>For Recipient 1:</b>		
ODT Recipient No:		
Virtual crossmatch (omitting the crossmatch test before transplant): Yes <input type="checkbox"/> No <input type="checkbox"/>		
	<b>Date(dd/mm/yyyy)</b>	<b>24hrTime(hh:mm)</b>
Time offer received		
Time agreed to proceed with a virtual crossmatch		
<b>If prospective pre-transplant crossmatch undertaken; donor tissues used:</b>		
Lymph node <input type="checkbox"/> Spleen <input type="checkbox"/> Pre-retrieval peripheral blood <input type="checkbox"/>		
Requirement for current recipient crossmatch sample: Yes <input type="checkbox"/> No <input type="checkbox"/>		
<b>If prospective pre-transplant crossmatch performed;</b>	<b>Date(dd/mm/yyyy)</b>	<b>24hrTime(hh:mm)</b>
Time staff arrived in laboratory to perform crossmatch		
Time <b>donor</b> crossmatch specimens received		
Time <b>recipient</b> crossmatch specimens received		
Time recipient crossmatch result reported		

<b>For Recipient 2:</b>		
ODT Recipient No:		
Virtual crossmatch (omitting the crossmatch test before transplant): Yes <input type="checkbox"/> No <input type="checkbox"/>		
	<b>Date(dd/mm/yyyy)</b>	<b>24hrTime(hh:mm)</b>
Time offer received		
Time agreed to proceed with a virtual crossmatch		
<b>If prospective pre-transplant crossmatch undertaken; donor tissues used:</b>		
Lymph node <input type="checkbox"/> Spleen <input type="checkbox"/> Pre-retrieval peripheral blood <input type="checkbox"/>		
Requirement for current recipient crossmatch sample: Yes <input type="checkbox"/> No <input type="checkbox"/>		
<b>If prospective pre-transplant crossmatch performed;</b>	<b>Date(dd/mm/yyyy)</b>	<b>24hrTime(hh:mm)</b>
Time staff arrived in laboratory to perform crossmatch		
Time <b>donor</b> crossmatch specimens received		
Time <b>recipient</b> crossmatch specimens received		
Time recipient crossmatch result reported		

<b>Reason for delay if any:</b>
<b>Number of back-up crossmatch performed simultaneously:</b> Virtual: Actual:

Form completed by (please print):

## Appendix 5: Questionnaire for recipient coordinator (recipient and transplant information)

National Audit of CIT

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### Kidney Transplant Information

#### For attending Recipient Coordinator

#### Notes:

1. Please complete this form for each potential deceased donor kidney and kidney + pancreas recipient who is admitted for transplant and for kidneys received but subsequently reallocated.
2. This form can be completed manually or electronically.
3. The study coordinator will greatly appreciate it if you could complete this form as clearly as possible and with black ink only.
4. When complete, please return the form to the coordinator centre in one of the following ways:

**Post:**

Sussie Shrestha  
C/O Ms Lorna Marson  
Consultant Surgeon  
Royal Infirmary of Edinburgh  
51 Little France Crescent  
Edinburgh  
EH16 4SA

**Fax No:** 0131 242 3617

**Email:** [sussie.shrestha@nhs.net](mailto:sussie.shrestha@nhs.net)

5. If you have any queries, please do not hesitate to contact the study coordinator, Ms Sussie Shrestha, on **07875500726 (mobile)**.

Date (dd/mm/yyyy):		
<b>DONOR DETAILS</b>		
ODT Donor No:		
<b>RECIPIENT DETAILS</b>		
ODT Recipient No:		
Hospital No:		
Kidney allocated: RIGHT <input type="checkbox"/> LEFT <input type="checkbox"/>		
Organ transplanted: Kidney only <input type="checkbox"/> Kidney & Pancreas <input type="checkbox"/>		
<b>RECIPIENT HOSPITAL</b>		
Transplant Centre:		
<b>Recipient Preparation:</b>	<b>Date(dd/mm/yyyy)</b>	<b>24hrTime(hh:mm)</b>
Time offer received		
Time offer accepted		
Time recipient contacted		
Time recipient arrived on ward		
Time kidney arrived at the hospital		
Recipient's mode of travel: Ambulance <input type="checkbox"/> Air <input type="checkbox"/> Patient's own <input type="checkbox"/> Taxi: <input type="checkbox"/>		
Recipient required haemodialysis pre-transplant Yes <input type="checkbox"/> No <input type="checkbox"/>		
If yes, time: Start:		
Finish:		
Time crossmatch result received		
Transplant cancelled Yes <input type="checkbox"/> No <input type="checkbox"/>		
If yes, reason:		
Kidney reallocated: Locally <input type="checkbox"/> Other centres <input type="checkbox"/> No <input type="checkbox"/>		
Reason for reallocation:		
<b>If reallocated locally, please complete a separate form for second recipient</b>		
If kidney transferred to a <i>different centre</i> :		
Time ODT informed		
Time organ collected		
<b>THEATRE TIMES</b>		
Theatre where transplant performed: Transplant theatre <input type="checkbox"/> Emergency theatre <input type="checkbox"/> Other <input type="checkbox"/>		
	<b>Date(dd/mm/yyyy)</b>	<b>24hrTime(hh:mm)</b>
Time theatre staff informed transplant can proceed		
Back table preparation time: Start:		
Finish:		
Time patient sent for		
Time patient arrived in anaesthetic room		
Time of start of surgery (knife to skin)		
Time kidney removed from ice for anastomosis		
Time of reperfusion		
<b>If SPK:</b>		
Back table preparation time for <b>pancreas</b> Start:		
Finish:		
Time start of surgery for <b>pancreas</b> (knife to skin)		
Time <b>pancreas</b> removed from ice for anastomosis		
Time of reperfusion of <b>pancreas</b>		
<b>Reason for delay if any:</b>		

Form completed by (please print):

## Appendix 6: Questionnaire for transport personnel (kidney transport information)

### Data from TFT

TRANSPORT TIMES		
Mode of transport of organ:		
Ambulance: <input type="checkbox"/>	Blue-light: Yes <input type="checkbox"/>	No <input type="checkbox"/>
Air: <input type="checkbox"/>		
Taxi: <input type="checkbox"/>		
	<b>Date(dd/mm/yyyy)</b>	<b>Time(hh:mm)</b>
Time organ collected		
Time of arrival at recipient centre		
Reason for delay if any:		

**Form completed by** (please print):

## Appendix 7: Questionnaire for transplant centre practices

### Transplant Unit Information

<b>Date:</b>
<b>Hospital Name:</b>
<b>Organs transplanted in the Unit:</b>
Liver <input type="checkbox"/> Kidney <input type="checkbox"/> Pancreas <input type="checkbox"/> Other <input type="checkbox"/>
Comments:
<b>Access to theatre for kidney transplant:</b>
Dedicated transplant theatre: In hours <input type="checkbox"/> Out of hours <input type="checkbox"/>
Access to emergency theatre only <input type="checkbox"/>
Comments:
<b>No. of consultant transplant surgeons active in DD kidney transplant in the Unit:</b>
<b>Local kidney allocation policy of transplant Unit:</b>
Recipients contacted one at a time <input type="checkbox"/>
Group of recipients identified <input type="checkbox"/>
Other <input type="checkbox"/>
Comments:
<b>Local allocation policy for DCD or any other locally allocated kidney and DBD kidney not used for 1<sup>st</sup> recipient:</b>
<b>Does the transplant unit have options for doing simultaneous kidney transplant for 2 kidneys if required?</b>
In hours <input type="checkbox"/> Out of hours <input type="checkbox"/>
<b>Would you cancel elective transplant for a DD kidney transplant?</b>
Yes <input type="checkbox"/> No <input type="checkbox"/>
<b>Does the unit have dedicated anaesthetic team for kidney transplant?</b>
In hours <input type="checkbox"/> Out of hours <input type="checkbox"/>
<b>No of dedicated beds available for DD kidney transplants:</b>
ICU beds HDU beds Ward beds
<b>What are the factors that affect your ability to take the patient to theatre for transplant?</b>
Surgeon availability <input type="checkbox"/>
Theatre availability <input type="checkbox"/>
Others (please specify): <input type="checkbox"/>



### MINIMISING COLD ISCHAEMIA TO MAXIMISE OUTCOMES IN DECEASED DONOR KIDNEY TRANSPLANTS

# Newsletter

Dear All

The first 4 months of the pilot study are now complete and it is being rolled out nationally. 4 transplant centres (Edinburgh, Glasgow, Cambridge and Nottingham), 5 H&I laboratories (Edinburgh, Glasgow, Cambridge, Oxford and Sheffield) and 2 SN-OD offices (Scotland and Eastern Organ Donation Services) participated in the pilot study, the main purpose of which was to ensure that the data collection forms are fit for purpose

#### Aims and Objectives

The aim of this study is to undertake a comprehensive review of factors contributing to cold ischaemia time in deceased donor kidney transplants across UK transplanting centres. A set of short data collection forms has been designed to document the timings around the retrieval process, organ transport, crossmatching, recipient preparation and surgery. This will allow us to investigate the current practice to identify the factors that contribute to prolonged cold ischaemic time along the kidney 'journey'. We will then pilot

the modification of these contributory factors and investigate the impact of such changes on CIT.

This study **includes** the following:

- Deceased donor (DBD and DCD) kidney transplants
- Deceased donor (DBD and DCD) kidney+pancreas transplants
- Adult and paediatric donors and recipients

This study **excludes** the following:

- Living donor kidney transplants
- Pancreas only transplants

#### Data collection sources

- H&I staff
- Recipient Coordinators and Transplant Surgeons/SpRs
- TFT
- ODT

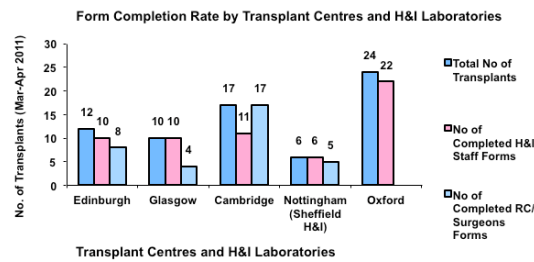
#### March and April 2011

A total of 45 deceased donor kidneys and kidney+pancreas were transplanted in March and April 2011 in the 4 centres that participated in the pilot study. 34 out of 45 (76%)

forms were completed and returned by the 4 transplant units. 59 forms were completed by the 5 H&I laboratories for a total of 69 transplants (86%).

We received a total of 21 forms for the same period from the 2 regional SN-OD offices, 7 from Scotland and 14 from Eastern Organ Donation Services which were 80 to 100 % complete.





### Extent of Completion of each form

Transplant Centre	RC Form	H&I Form
Edinburgh	54-78%	56-100%
Glasgow	57-92%	78-100%
Cambridge	73-96%	92-100%
Nottingham	92-100%	N/A
Sheffield	N/A	85-100%
Oxford	N/A	62-100%

### Current Status

The study coordinator has visited 12 transplant centres and 12 H&I laboratories, so far, out of which 11 transplant centres and all the H&I laboratories have agreed to sign up for the national study.

#### Transplant Centres

- 1 Royal Infirmary, Edinburgh
- 2 Western Infirmary, Glasgow
- 3 Addenbrooke's Hospital, Cambridge
- 4 City Hospital, Nottingham
- 5 Churchill Hospital, Oxford
- 6 Leicester General Hospital, Leicester
- 7 Royal Liverpool University Hospital, Liverpool
- 8 Manchester Royal Infirmary, Manchester
- 9 The Royal London Hospital, London
- 10
- 11 Queen Elizabeth Hospital, Birmingham
- 12 Guy's Hospital, London

#### H&I Laboratories

- Royal Infirmary, Edinburgh  
 Gartnavel General Hospital, Glasgow  
 Addenbrooke's Hospital, Cambridge  
 NHSBT, Sheffield  
 Churchill Hospital, Oxford  
 Leicester General Hospital, Leicester  
 Royal Liverpool University Hospital, Liverpool  
 Manchester Royal Infirmary, Manchester  
 The Royal London Hospital, London  
 St James's University Hospital, Leeds  
 NHSBT, Birmingham  
 Guy's Hospital, London



More visits are planned for the remaining 11 transplant centres and 8 H&I laboratories in the near future. A summary report of individual transplant centre and H&I laboratory will be sent out on a regular basis to all the participating centres.

Thank you

Kind regards  
Sussie

Sussie Shrestha  
Clinical Research Fellow  
Royal Infirmary of Edinburgh  
51 Little France Crescent  
Edinburgh  
EH16 4SA

Email: [sussie.shrestha@nhs.net](mailto:sussie.shrestha@nhs.net)  
Tel: 07875500726 (Mobile)

### Acknowledgements

We would like to express our thanks to all those who supported the project. Please let me know if you require any further information regarding the project.

## Appendix 9: Newsletter 2



### MINIMISING COLD ISCHAEMIA TO MAXIMISE OUTCOMES IN DECEASED DONOR KIDNEY TRANSPLANTS

# Newsletter

Dear All

Welcome to the second newsletter of the national cold ischaemic time (CIT) project for six months between June and November 2011. The project is now well underway nationally with 21 transplant centres and 19 Histocompatibility and Immunogenetics (H&I) laboratories signed up to it.

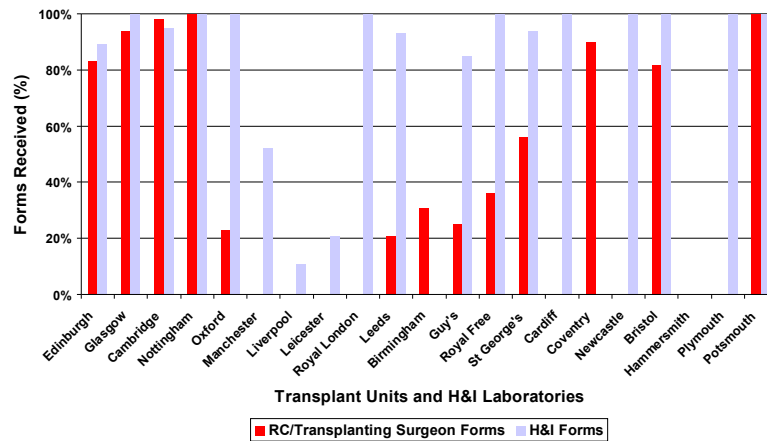
We continue to collect data from the following sources:

1. ODT / Specialist Nurse for Organ Donation (SNODs)
2. Transport service providers
3. H&I staff
4. Recipient coordinators (RCs) and transplanting surgeons

Donor data is collected on core donor data from ODT as well as from the SNODs at Scottish and Eastern Organ Donation Services. Transport data is also collected from the ODT.

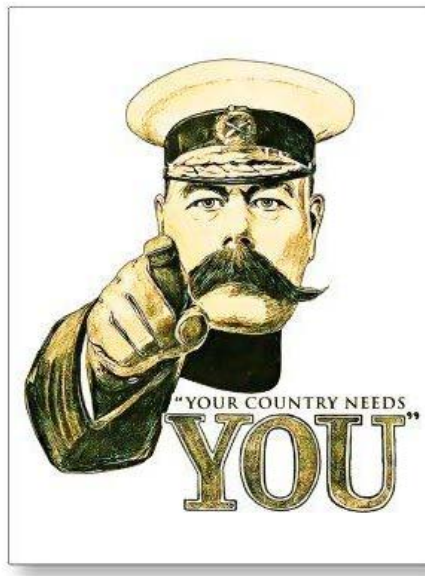
A total of 851 deceased donor kidney only and SPK transplants were performed in the United Kingdom within the 6 month period. In addition to the data collected from the ODT, we received some data for 570 out of the 851 transplants, ie., 66.98% of the total transplants in the period.

Contribution to the Project by Centres Expressed as % of Completion of Forms by Recipient Coordinators / Transplanting Surgeons and H&I Staff for 6 months since June 2011 (or since joining the project, if later)



### Current Status

All units have been approached for the project. 21 out of 23 transplant units have been visited and a further unit has agreed to participate without a visit. 15 out of 20 H&I laboratories are fully engaged with the project and are returning forms. 13 out of 23 transplant units (recipient coordinators and transplant surgeons) are also fully engaged.



Thank you

Kind regards  
Sussie

Sussie Shrestha  
Clinical Research Fellow  
Royal Infirmary of Edinburgh  
51 Little France Crescent  
Edinburgh  
EH16 4SA

Email: [sussie.shrestha@nhs.net](mailto:sussie.shrestha@nhs.net)  
Tel: 07875500726 (Mobile)